A. M. A.
ARCHIVES OF
NEUROLOGY AND PSYCHIATRY

OCTOBER 1952
VOLUME 68 NUMBER 4

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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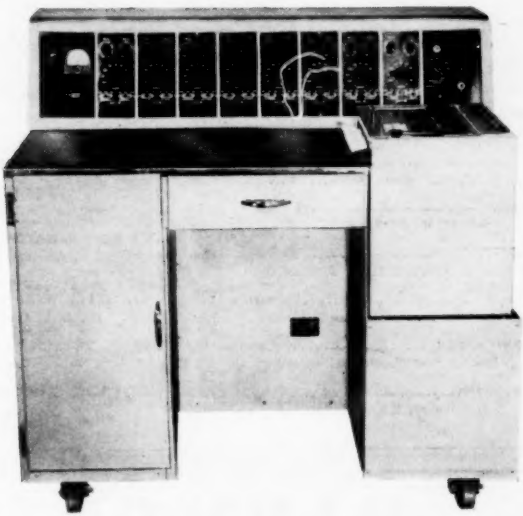

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VOLUME 68 OCTOBER 1952 NUMBER 4

ARCHITECTONIC DISTRIBUTION OF ACETYLCHOLINESTERASE IN THE FRONTAL ISOCORTEX OF PSYCHOTIC AND NONPSYCHOTIC PATIENTS

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NEW YORK
AND
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WHETHER study of the physics and chemistry of the brain can contribute importantly to fuller understanding of the nature of mental illness is a question to which present knowledge furnishes no clear answer. With certain simple exceptions, translations are not now possible between verifiable assertions in physical language concerning that structure of spatiotemporal events which is the brain in action and those in psychological language that describe behavior and, within the framework of psychodynamics, postulate its determinants. Both systems of assertions refer to aspects of single sets of occurrences, and, a priori, there is no reason for devaluation or exclusion of either as a means toward greater understanding of the phenomena of psychiatry.

Classic neuropathology has sought unavailingly for a characteristic brain "lesion" in the major psychoses. Innumerable claims to the contrary, it must be acknowledged that at the level of histopathology and cytopathology no unique, characteristic, or consistent anatomical change has yet been found for schizophrenia, manic-depressive psychosis, or involutional psychosis.

Other levels, however, remain for comparative description. These include, on the one hand, description of neurones and neuroglia as physicochemical systems (including the physical chemistry of nervous excitations) and, on the other, study of the relationships and interactions of similar units organized into aggregates that define the temporal order and spatial distribution of the excitations which constitute the action of the brain.

At the first, or molecular, level, a role of critical importance is played by the intracellular enzymes which direct and control the organic reactions resulting in the energy transformations of cellular metabolism. In the central nervous system their performance is directly related to the excitation and inhibition of neurone units

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

and, therefore, is part of the causal chain establishing those synchronous, and spatially and temporally dispersed, electrochemical events within the brain that have correspondence with the organism's behavior. Accordingly, the comparative quantitative study of cerebral enzymes involved in the general or special metabolism of the nervous system is one appropriate way of searching for evidence of chronic alterations in cellular function in the brains of persons who exhibit abnormal behavior. For such study a basic assumption of tissue biochemistry is necessarily made, namely, that under the standard conditions of assay the comparative activities of enzymes measure the potential rate of turnover of the particular intracellular metabolic reaction which each governs.

The cerebral cortex is a part of the brain of unquestionable, though not exclusive, importance for enzymatic and other physicochemical description in relation to mental illness. Moreover, its stratified architecture makes it uniquely suitable for studies aimed at simultaneous advancement upon a second biological frontier, that of correlating the histological and biochemical aspects of tissue structure. This can be done by means of the ingenious methods for alternate frozen-section sampling and ultramicroquantitative analysis, developed by Linderstrøm-Lang and Holter.[1] These and related methods are being used in the McLean Hospital Research Laboratory for determining in the rat cerebral cortex the quantitative distribution within the cytoarchitectonic layers of certain enzymes of importance in the metabolism of the nervous system and for enabling interpretation of the findings in terms of fine anatomical cortical structure.[2]

Similar studies are also in progress upon biopsy specimens of human cortex. The use of biopsy, rather than necropsy, material is necessary for studies upon most human cerebral enzymes in order that the tissue may have approximate biochemical equivalence and the analytical results validity for comparison from patient to patient. For such inquiries, the ultramicrotechniques of quantitative histochemistry have added advantages, since they enable acquisition of a maximum of information from small tissue samples, provide for accurate neuropathological control of all observations, and presumably furnish a maximum opportunity for the observing of relatively subtle changes.

During 1948, a pilot study was done upon the activity and architectonic distribution of acetylcholinesterase in biopsy specimens of human cortex. These specimens were obtained during the course of prefrontal lobotomy from patients with various forms of psychiatric illness or intractable pain. An attempt was made to select patients with clearly defined clinical syndromes and to obtain the biopsy material under as carefully controlled and standardized conditions as possible. Acetylcholinesterase was studied as an index of the potential rate of turnover of the enzyme system that metabolizes acetylcholine. The exact role of this compound in the activation and propagation of nerve impulses, or in their transsynaptic passage, is,

1. Linderstrøm-Lang, K.: Distribution of Enzymes in Tissues and Cells, Harvey Lect. **34**:214, 1939; Bull. New York Acad. Med. **15**:719, 1939. Holter, H., and Linderstrøm-Lang, K.: Micromethods and Their Application in the Study of Enzyme Distribution in Tissues and Cells, Physiol. Rev. **31**:432, 1951.

2. (*a*) Pope, A.; Ware, J. R., and Thomson, R. H.: Quantitative Histochemical Distribution of Enzymes in Cytoarchitectural Layers of Cerebral Cortex, Federation Proc. **9**:215, 1950. (*b*) Pope, A.: Quantitative Distribution of Dipeptidase and Acetylcholine Esterase in the Architectonic Layers of Rat Cerebral Cortex, J. Neurophysiol. **15**:115, 1952.

of course, controversial; but that it is one of critical importance in nervous excitations can hardly be doubted. These experiments have already been summarized in part.[3] In this paper, their nature, outcome, and possible significance will be described in full.

MATERIAL AND METHODS

Clinical Part

The cortical biopsy specimens were obtained, for the most part, from patients undergoing prefrontal lobotomy at the Boston Psychopathic Hospital. These were persons hospitalized under the Department of Mental Health of Massachusetts and therefore representative of a state-hospital population. They were selected for study in accordance with a number of criteria, of which the chief was how perfectly each patient typified the standard for his assigned diagnostic classification. The drawbacks and limitations of the designations of psychiatric diagnoses as reference standards for description of clinical behavior were recognized, but for this preliminary study no attempt was made to characterize or classify various facets of behavior or to interpret meanings in dynamic terms. An effort was made to obtain specimens from a series of patients exemplifying as many as possible of the main groups and subgroups of classic psychiatric diagnoses.

A second criterion for selection was absence of evidence indicating any progressive destructive pathological process in the central nervous system. Each patient received a thorough neurological examination, and, in some cases possible "organic" defects were further excluded by examination of the cerebrospinal fluid, roentgenographic studies of the skull, pneumoencephalography, psychometric tests, or electroencephalography. It was thought that all the patients studied represented cases of the so-called functional psychoses and psychoneuroses. With one exception, the patients were between 20 and 50 years of age. As far as possible, only patients who had had no or a minimum of convulsion therapy were selected. Inasmuch as few patients became candidates for lobotomy who had not had a trial of shock therapy, this selection was difficult, but, with two exceptions, none had received insulin or electric shock for a number of months prior to operation.

In addition, cortical biopsy specimens were obtained from two patients lobotomized at the New England Baptist Hospital for intractable pain due to carcinomatosis.

Important clinical information upon each patient is summarized in Table 1. The 17 patients included 10 with various forms of schizophrenia, 3 with crippling psychoneuroses, 2 suffering from severe somatic pain, and 1 each with a condition classified as paranoid condition and manic-depressive psychosis, hypomanic phase.

Clinically, they fell into two principal categories. The first was comprised of patients who, though certainly not to be regarded as "normal" for comparative purposes, were at least to be considered "nonpsychotic." The groups included the two patients with intractable pain and the three classified as psychoneurotic. None of the latter had ever shown truly psychotic behavior or required protracted hospitalization. They all had insight and were in good contact at the time of operation. The patients with intractable pain were far from ideal "controls," having drug addiction, malnutrition, and anxiety in addition to their somatic illness. Nevertheless, the patients with pain and those with psychoneurosis did constitute a relatively normal group with respect to observable behavior, in contrast to patients of the second category. This was made up of patients who were frankly psychotic. Most of them were patients with chronic deteriorated schizophrenia who were regressed and deeply disturbed. Their illness was classified as schizophrenia—hebephrenic, catatonic, or other types. Included with the psychotic group were one patient with paranoid schizophrenia, the hypomanic patient, and the patient with the illness diagnosed as paranoid condition.

Within these two categories, there were certain patients of comparable ages (32 to 47) who otherwise were widely divergent with respect to clinical status, thus forming two sharply contrasting subgroups of "selected" cases (with asterisk in Table 1). One subgroup was comprised of four of the clearly nonpsychotic patients who fell within the stated age range. The

3. Pope, A.; Meath, J. A.; Caveness, W. F.; Livingston, K. E., and Thomson, R. H.: Histochemical Distribution of Cholinesterase and Acid Phosphatase in the Prefrontal Cortex of Psychotic and Non-Psychotic Patients, Tr. Am. Neurol. A. **74**:147, 1949.

other included five of the deeply psychotic deteriorated schizophrenic patients who had in common onset of their illness at an early age (18 to 22 years) and a history of relentless progression of the schizophrenic process, requiring long and continuous hospitalization (8 to 17 years) and leading to severe dilapidation and withdrawal at the time of operation. These "selected" nonpsychotic and psychotic subgroups of patients were thought to represent roughly the ends of the spectrum of psychiatric illnesses on the basis of the single criterion, namely, degree of preservation of personality integration.

Operative Technique.—All the patients received standard preoperative medication, consisting of ¼ to ⅙ grain (15 to 10 mg.) of morphine sulfate and 1/150 grain (0.12 mg.) of atropine

TABLE 1.—*Summary of Clinical Data*

Patient	Sex	Age	Preoperative Diagnosis	Duration of Illness, Yr.	Continuous Hospitalization, Yr.	Convulsion Therapy: Agent	Convulsion Therapy: No. of Shocks	Convulsion Therapy: Year	Operative Anesthesia
*D. A.	F	37	Schizophrenia, hebephrenic	17	15	Insulin	..	1938	Thiopental sodium, 0.8 gm.
H. S.	M	45	Paranoid condition	12	2	EST†	60	1947	Local
A. J.	F	61	Schizophrenia, catatonic	18	18	None	..	....	Local
*E. V.	F	37	Schizophrenia, catatonic	15	15	Metrazol®	20	1938	Local
*R. L.	M	45	Intractable pain (cancer)	..	..	.....	..	....	Thiopental sodium, 0.5 gm.
E. M.	F	38	Manic-depressive, manic	13	1	EST	20	1945	Thiopental sodium, 0.9 gm.
*E. C.	F	47	Psychoneurosis, conversion hysteria	18	..	EST	19	1947	Thiopental sodium, 0.8 gm.
H. C.	M	31	Schizophrenia, other types	8	8	Metrazol® EST	.. 7	1940-1945 1946	..... Thiopental sodium, 1.5 gm.
*M. K.	F	37	Psychoneurosis, obsessive-compulsive	10	..	None	..	....	Thiopental sodium, 0.75 gm.
*R. E.	F	41	Schizophrenia, other types	20	8	Insulin	..	1945	Thiopental sodium, 0.5 gm.
C. S.	M	53	Intractable pain (cancer)	..	..	.....	..	....	Thiopental sodium, 0.5 gm.
K. McL.	F	35	Schizophrenia, paranoid	4	..	Insulin	8	1946	Thiopental sodium, 0.5 gm.
*V. R.	F	33	Psychoneurosis, obsessive-compulsive	11	..	None	..	....	Thiopental sodium, 0.8 gm.
R. M.	F	44	Schizophrenia, catatonic	9	?	EST EST EST EST EST	9 8 24 23 7	1943 1945 1946 1947 1948	Thiopental sodium, 0.3 gm.
*J. K.	M	32	Schizophrenia, catatonic	10	10	None	..	....	Thiopental sodium, 1.5 gm.
*G. F.	F	35	Schizophrenia, catatonic	17	17	EST	2	1946	Local
A. T.	M	20	Schizophrenia, catatonic	5	4	EST Insulin	11 ..	1945 1947	Thiopental sodium, 1.25 gm.

* The starred patients are those who rigidly fulfilled the clinical criteria according to which patients were assigned to "selected" psychotic and nonpsychotic categories, as explained in the text.
† EST indicates electric shock therapy.

sulfate. Four patients were operated upon, with use of local anesthesia only, consisting of infiltration of the scalp with 1% procaine hydrochloride. The remainder received 0.5 to 1.5 gm. of thiopental (pentothal®) sodium intravenously and were under general anesthesia for 15 to 45 minutes before removal of the biopsy specimen.

Prefrontal lobotomy was performed according to the technique of Poppen.[4] After longitudinal incision of the scalp 3.5 cm. from the midline, the coronal suture was identified, and exactly 3.0 cm. anterior to it the center of a trephine button 2.5 cm. in diameter was placed. After reflection of a small dural flap, the major portion of the presenting cortical gyrus was isolated by careful dissection of adjacent gyri. Dissection was carried down to depth of 1.5 cm. or more and well into the underlying white matter. Bleeding was controlled by remote coagulation or clipping of significant blood vessels and by use of very small cotton pads. After lateral isolation, the specimen was lifted out with a pituitary spoon and transferred immediately to a refrigerated container, in which it was brought to the McLean Hospital Research Laboratory. With this technique, sizable biopsy specimens of uninjured and essentially undisturbed cortex were obtained.[5]

4. Poppen, J. L.: Technique of Prefrontal Lobotomy, J. Neurosurg. **5**:514, 1948.

5. Miss Celia Lauricella gave careful assistance in the immediate handling of these specimens.

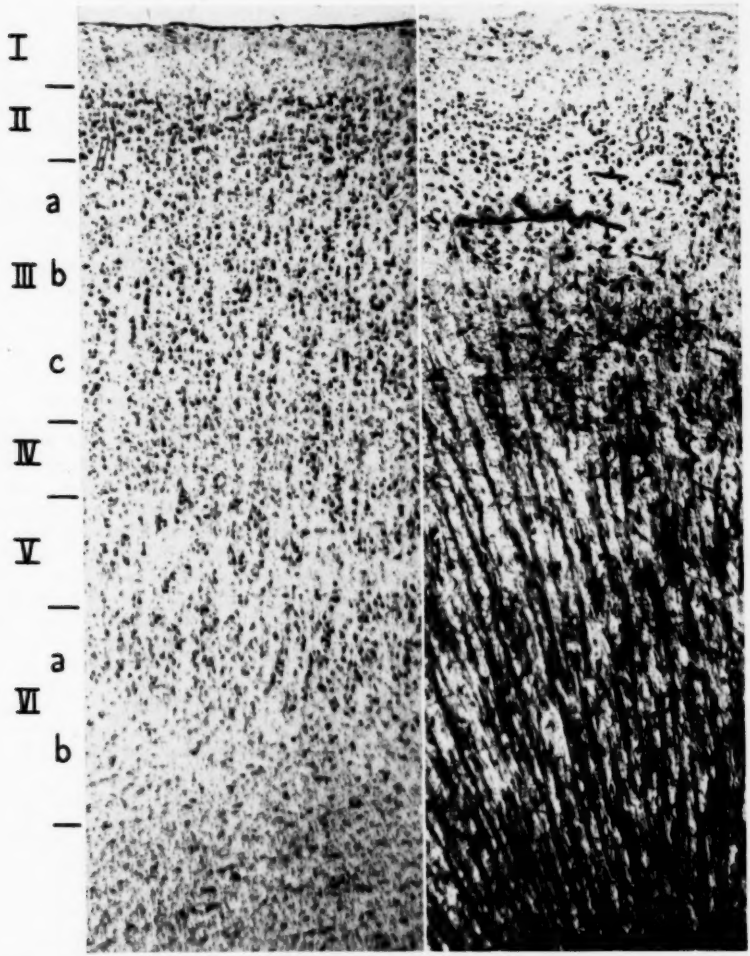

Fig. 1.—Cytoarchitecture and myeloarchitecture of human frontal isocortex (Area 9 of Brodmann, FD_M of von Economo, IEf_8 of Bailey and von Bonin). Lamination is indicated in Nissl (left) and Weigert-Pal (right) preparations (20 μ; 40 magnifications). In the present series the cortex varied in total thickness from 2,400 to 3,200 μ. Layer I averaged 7.7%; Layer II, 8.3%; Layer III, 29.0%; Layer IV, 10.0%; Layer V, 16.7%, and Layer VI, 28.3% of the total width. In differential cell counts in four Nissl preparations, the numbers of nerve cells per oil immersion field averaged 3 in Layer I, 19 in Layer II, 9 in Layer III, 18 in Layer IV, 7 in Layer V, and 9 in Layer VI. Similarly, the sum of the astrocytes and oligodendrocytes was 10 in Layer I, 9 in Layer II, 9 in Layer III, 10 in Layer IV, 7 in Layer V, and 12 in Layer VI. The external line of Baillarger corresponds with cytoarchitectonic layers IIIc-IV; the internal line, with the V-VI junction. Horizontal myelinated fibers are moderately numerous in Layer I. The Kaes-Bechterew line (Layer IIIa) is identifiable, but not conspicuous.

The specimens were derived from that portion of the frontal lobe designated as Area 9 by Brodmann, Area FD_m by von Economo and Koskinas[6] and Area IEfs by Bailey and von Bonin,[7] in their recent comprehensive study of the human cortex.

The cytoarchitecture and its myeloarchitectonic equivalent are shown and described in Figure 1. The structure is that of homotypical, eugranular frontal isocortex, exactly that described as "typical eulaminate isocortex" by Bailey and von Bonin.[7] In detail, it corresponds with their block VI, and with the recent descriptions for Area 9 by Mettler[8] and for FD_m by Conel.[9]

Experimental Part

Immediately after receipt in the laboratory, a portion of each biopsy specimen was dissected from the free surface of a gyrus which grossly presented a relatively flat pial surface and uniform thickness of the underlying gray matter. This block was then frozen, stored in a dry ice chest (—78 C.), and used subsequently for the acetylcholinesterase experiments.[10] The rest of each specimen was divided into blocks, which were placed in fixatives suitable for standard neurohistological stains.[11]

For determination of the cytoarchitectural distribution of acetylcholinesterase, the frozen block was subjected to serial frozen-section sampling and alternate enzyme assay and histological study, according to a modification of the method of Linderstrøm-Lang and Mögensen,[12] which has already been described in detail.[2b] The sampling procedure was carried out in a cold room maintained at —12 C. From the frozen block a uniform cylinder of cortex, 2 mm. in diameter, was punched out the long axis of which was perpendicular to the plane of the pial surface. With a rotary microtome the cylinder was then cut from pia to white matter into uniform, consecutive, horizontal frozen sections, each 40 μ in thickness. The first section cut, which was usually incomplete, was discarded. Thereafter, sections were studied in consecutive groups of four each. The first section of each group was placed upon an albuminized microscope slide, thawed in place, fixed in alcohol and formalin, and stained with thionine at pH 4.5 by the modification of Nissl's method developed by Windle, Rhines, and Rankin.[13] The third section was desiccated over calcium chloride ($CaCl_2$), and its dry weight was subsequently determined by means of a Lowry quartz-fiber ultramicrobalance.[14] The second and fourth sections were used respectively as experimental and autolysis control preparations for assay of acetylcholinesterase activity by the ultramicrotitrimetric technique of Glick.[15] Each section

6. von Bonin, G.: Essay on the Cerebral Cortex, Springfield, Ill., Charles C Thomas, Publisher, 1950.

7. Bailey, P., and von Bonin, G.: The Isocortex of Man, Urbana, Ill., University of Illinois Press, 1951.

8. Mettler, F. A.: Cytoarchitecture, in F. A. Mettler, Editor: Selective Partial Ablation of Frontal Cortex, New York, Paul B. Hoeber, Inc., 1949, Chap. 5, pp. 48-78.

9. Conel, J. L.: The Postnatal Development of the Human Cerebral Cortex, Vol. IV: The Cortex of the Sixmonth Infant, Cambridge, Mass., Harvard University Press, 1951.

10. These blocks were stored at this temperature for 0 to 10 days before use. Control experiments upon rat cerebral cortex showed that no appreciable loss of acetylcholinesterase activity occurred in specimens stored at this temperature for as long as two months. There was no correlation between the length of time that these human specimens were stored and the mean acetylcholinesterase activity per specimen.

11. A small portion of each specimen had already been dissected in the operating room immediately after removal and placed in formalin-ammonium bromide fixative for neuroglial preparations.

12. Linderstrøm-Lang, K., and Mögensen, K. R.: Histological Control of Histochemical Investigations, Compt. rend. trav. lab. Carlsberg, série chimique **23**:27, 1938.

13. Windle, W. F.; Rhines, R., and Rankin, S.: A Nissl Method Using Buffered Solutions of Thionine, Stain Technol. **18**:77, 1943.

14. Lowry, O. H.: A Simple Quartz Torsion Balance, J. Biol. Chem. **152**:293, 1944.

15. Glick, D.: Studies on Enzymatic Histochemistry: A Micro-Method for the Determination of Cholin Esterase, and the Activity, pH Relationships of This Enzyme, J. Gen. Physiol. **21**:289, 1938.

was placed in a microtube and extracted at 4 C. for 24 hours in 10.3 cu. mm. of 30% glycerin. After the addition of 12.2 cu. mm. of 0.4% aceylcholine bromide in 0.1 M barbital buffer, pH 8.3, the tubes were incubated at 37 C. for one hour. Acetylcholinesterase activity was then terminated by the addition of 73.1 cu. mm. of 0.1% physostigmine sulfate solution containing bromothymol blue. The contents of each tube were then back-titrated with 0.05 N HCl to match a color standard at pH 6.2. The difference in titer between the experimental tube and its corresponding control, in which contact between enzyme extract and substrate was prevented during the period of hydrolysis, was equivalent to the moles of acetylcholine split by enzymatic action per cortical section. The results were expressed in terms of this difference in titration value of 0.05 N HCl per microgram of dry weight of the adjacent, weighed section of each experimental series. For each experiment the activities thus expressed were recorded with reference to the theoretical depth, in microns, beneath the pial surface of the experimental samples. Since the first 40-μ section cut was discarded, and the second used for histological study, the first section for acetylcholinesterase determination theoretically centered at a depth of 100 μ and the others, in order, at intervals of 160 μ. The cortex varied in thickness among the specimens from 2,400 to 3,200 μ, so that among the individual experiments from 15 to 20 series of four sections each were obtained.

The widths of the cytoarchitectonic layers in the cortical cylinders were estimated in two ways. The layers of each horizontal Nissl preparation were identified directly. In addition, the frozen block, from which the experimental cylinder had been derived, was thawed and fixed in 10% formalin. Vertical frozen sections were then cut from the surface immediately adjacent to the site of the cylinder and stained by Hortega's modification of Cajal's reduced-silver method for neurofibrils and axis-cylinders. In these preparations, the widths of the cytoarchitectural layers, in microns, were measured directly by means of the calibrated stage of a Leitz Ortholux microscope. Such preparations showed minimal shrinkage artifacts and, in addition, made it possible to examine both cellular architecture and neuropil in material immediately adjacent to the sample used for enzyme study. By comparison of the measured layer widths and the theoretical depths of the horizontal sections whose layers could be identified, it was possible to estimate the layer widths in the cortical cylinder from which the series of sections for acetylcholinesterase assay were derived, and thus for each experiment to establish the cytoarchitectonic distribution of the enzyme.

Certain standard neurohistological preparations were made from suitably fixed blocks of each biopsy specimen.[16] In all cases these included, in addition to the aforementioned sections, other Windle-Nissl and Hortega neurofibrillar preparations, sections stained by the Cajal gold chloride-mercury bichloride method for astrocytes, and Hortega silver-carbonate impregnations for the oligodendroglia. In some instances preparations for myelin sheaths and intracellular lipid were also made. This neuropathological material was reviewed carefully for signs of acute or chronic abnormalities in both neurones and neuroglia and for any other evidence of past or present destructive processes involving the elements of the cerebral cortex. The oligodendroglial preparations represented partial overlap of a parallel study, which will be reported in detail elsewhere.

RESULTS AND COMMENT

The results of 17 experiments upon the cortical activity and architectonic distribution of acetylcholinesterase are presented in Table 2. For each experiment, the enzyme activities, expressed as titration values in cubic millimeters of 0.05 N HCl per microgram of dry weight, are recorded in relation to the theoretical depth of each sample beneath the pial surface and to the cytoarchitectonic layer from which each serial sample was obtained. Again, for each specimen, the average activity, similarly expressed, for the cortex as a whole is indicated. Finally, in the last column, the mean activities of corresponding serial groups from all the experi-

16. Miss Ruby Thomson did the technical preparation of the histological material used in this study.

TABLE 2.—*Acetylcholinesterase Activity in Relation to the Cytoarchitecture of Human Frontal Isocortex*

Acetylcholinesterase Activity (Cu. Mm. 0.05 N HCl per Microgram Dry Weight × 100)

Series	Depth (μ)	Layer	D.A.	H.S.	A.J.	E.V.	R.L.	F.M.	E.C.	H.C.	M.K.	R.E.	C.S.	K.McL.	R.M.	J.K.	V.R.	G.F.	A.T.	Average
1	100	I	4.4	5.7	4.8	6.9	3.1	1.8	1.1	3.5	3.2		3.3	0.0	4.2	3.7			3.0	3.5
2	260		6.0	2.3	3.3	5.5	1.2	0.0	0.7		1.6	2.2	1.9	0.0	4.5	2.7	0.9	2.6	0.0	1.8
3	420	II	1.7	5.4	7.6	6.4	2.4	2.4	1.3	3.3	0.0	3.2	1.5	1.7	1.5	0.3	1.4	3.5	2.1	2.7
4	580		2.8	3.4	1.2	2.4	2.0	1.3	0.0	3.0	0.6	2.2	1.4	1.0	2.7	2.1	2.2	1.6		1.9
5	740		0.0	4.7	0.9	3.4	3.1	1.4	0.3	4.5	1.6	3.1	3.9	1.7	3.7	1.7	2.0	1.5	0.9	2.3
6	900	III	3.0	2.1	5.0	5.9	2.1	1.6	1.4	4.7	1.6	1.6	2.3	1.6	2.4	1.9	0.6	2.6	0.9	2.4
7	1,060		4.3	2.0	3.1	0.9	4.6	1.7	1.1	4.7	0.9	3.5	1.4	1.9	1.5	1.7	1.5	1.9	1.8	2.3
8	1,220		3.2	1.0	1.5	2.6	3.2	2.0	1.5	5.7	0.6	0.6	1.5	1.5	0.6	1.7	2.4	1.9	2.4	2.0
9	1,380		3.0	1.5	3.9	0.6	1.4	0.5	0.9	4.7	1.2	2.5	2.1	2.4	1.8	1.8	1.3	2.0	0.0	1.9
10	1,540	IV	2.0	2.2	5.0	3.8	0.0	1.5	0.3	3.7		3.6	0.3	1.7	1.2	0.6	0.6	0.0	0.6	1.7
11	1,700		4.9	3.2	3.1	0.9	1.4	1.4	0.5	0.7	1.2	2.1	0.6	2.2	2.5	0.0	2.1	2.6	0.0	1.7
12	1,860	V	0.9	6.1	4.5	3.5	0.9	1.8		5.4	1.5	3.0	1.4	1.4	2.1	1.9	1.5	0.0	0.5	2.3
13	2,020		2.1	3.6	1.3	2.6	1.7	1.6	1.1	3.3	1.2		1.3	1.7	1.9	2.4	1.9	0.3	0.0	1.8
14	2,180		2.6	3.9	1.4	2.2	0.8	2.9	0.0			1.1	2.4	1.1	2.6	1.4	2.5	2.2	0.3	1.8
15	2,340		4.9	2.0	0.3	4.1	3.6		0.8	2.4		1.1	0.0		0.6	0.3	1.3	0.9	0.2	1.6
16	2,500	VI	1.1	2.8	0.0	0.8	0.0	0.3	1.7	1.6		1.1	0.0		0.5	0.0	0.0	1.8	0.0	0.8
17	2,660			0.3	0.2	0.7	0.0	1.3	1.5	0.6			0.0		0.3	0.6	0.8	2.2		0.7
18	2,820			1.4		0.9	2.0	0.0	0.0	0.7						0.6		1.8		0.9
19	2,980	White Matter		4.4		2.1	0.2	1.3	0.2	0.6								0.7		1.4
20	3,140			1.7		1.9	0.0	0.6	0.0	0.4										0.8
Mean for cortex			2.6	3.0	2.8	2.9	1.8	1.3	0.8	3.3	1.3	2.2	1.5	1.4	2.1	1.4	1.4	1.7	0.9	

ments are recorded. In Figure 2 these averages of the values for acetylcholinesterase activity found in equivalent serial sections from each experiment are plotted as a function of their theoretical depth beneath the cortical surface, and the relationship of the resulting cortical distribution pattern of the enzyme to the averaged widths of the architectonic layers is shown. For reasons previously analyzed,[2b] such a composite distribution curve tends to be flattened as compared with the curve for any given experiment; nevertheless, it does retain the principal recurrent features found in individual experiments.

These results will be discussed under two headings: first, the nature and significance of the intracortical distribution of acetylcholinesterase, and, second, cor-

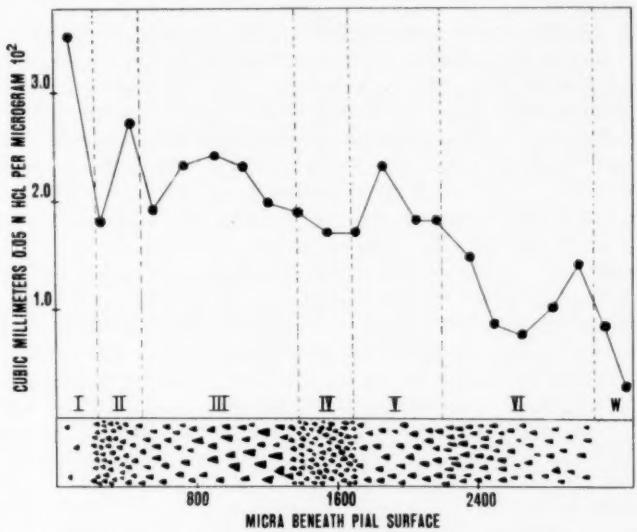

Fig. 2.—Cytoarchitectural distribution of acetylcholinesterase in human frontal isocortex. The sketch at the bottom of the figure shows architectural features in Nissl preparations and laminar designations.

relations between the average acetylcholinesterase activities of the various specimens and the respective clinical diagnoses.

Architectonic Distribution of Acetylcholinesterase.—Inspection of Figure 2 and of the results presented in Table 2 reveals a number of characteristic features of the cytoarchitectural distribution of this enzyme in frontal isocortex which recurred more or less regularly among the individual experiments. In 12 of 14 experiments in which satisfactory samples of the plexiform layer (Layer I) were obtained there was a definite peak of acetylcholinesterase activity at this level. Similarly, in 12 of 14 experiments the enzyme was relatively less abundant in Layer II, especially in Layer IIa. This was followed in 13 of 16 experiments by a second peak of activity at approximately the level of the junction of Layer II and Layer IIIa. In virtually all experiments (15 of 17) there was a broad zone of relatively high acetylcholin-

esterase activity in the midzone of Layer III, which in over half the experiments appeared as a doublet with one peak of activity at a depth of about 800 μ and a second peak closer to a depth of 1,200 μ. In 12 of 16 experiments there was distinctly less acetylcholinesterase in Layer IV. In most instances (14 of 17 experiments) another band of increased activity was found at about the middle of Layer V. In Layer VIa a smaller peak occurred in 11 of 15 experiments; this was followed by a region of diminished activity throughout the midzone of Layer VI (9 of 13 experiments) and, in some instances (5 of 12 experiments), by another definite peak in Layer VIb, close to the border of the white matter. In each of the five experiments in which the sampling furnished sections of white matter, the latter showed very much less acetylcholinesterase activity than was found throughout the gray cortex.

Thus, in human frontal isocortex acetylcholinesterase activity is high, relative to that in immediately adjacent zones, in cytoarchitectonic Layers I, the II-IIIa junction, and the midzones of Layers III and V, and equally definite levels of relatively low activity occur in Layers IIa and IV and the major portion of Layer VI. In view of the species and areal differences, it is perhaps remarkable that this architectural pattern of distribution is so similar to that shown by the same enzyme in the somatosensory field of rat isocortex, where it has been found to be most active in Layer I, the II-IIIa junction, and Layers IIIb, Va, and Vc, and close to the border of the white matter.[2b]

In the rat somatosensory cortex, in which the exact morphology of the cortical cells, including their axons and dendrites, and of the afferent fibers has been completely determined by Lorente de Nó,[17] it was possible to analyze the enzyme-distribution pattern in terms of the composition of the cortical axonal and dendritic plexuses, to show that in general the activity of the enzyme parallels the probable density and degree of arborization of these plexuses, and to suggest that in the cerebral cortex acetylcholinesterase may be located at the surface of the conducting and transmitting structures. It is altogether probable that the correspondence between the architectonic distribution of the enzyme in rat postcentral and human frontal cortex means that in each type the pattern is open to similar interpretation. Unfortunately, interpretations of the sort attempted for postcentral isocortex, in terms of the exact distribution of cortical axons and dendrites, cannot be made for frontal isocortex, since knowledge of the anatomical fine structure of this region is fragmentary.[17b] Nevertheless, certain tentative conclusions may perhaps be made.

Acetylcholinesterase activity is higher in Layers I to V than in Layer VI and is especially great in Layer I. In general, the activity of the enzyme is relatively high at levels which in Nissl preparations are comparatively acellular and in myelin-sheath stains are comparatively lacking in large-caliber myelinated axons. These are levels at which the finer and more extensively arborized axonal and dendritic plexuses must have their greatest development and, therefore, make a relatively great contribution to the mass of the tissue. Such considerations suggest that in human cortex acetylcholinesterase activity is associated primarily with the neuropil

17. Lorente de Nó, R.: (*a*) La corteza cerebral del ratón, Trab. lab. invest. biol. Univ. Madrid **20**:41, 1922; (*b*) Cerebral Cortex: Architecture, Intracortical Connections, in Fulton, J. F.: Physiology of the Nervous System, Ed. 3, New York, Oxford University Press, 1949, Chap. 15, pp. 288-315.

rather than with nerve cell bodies, a relationship that has already been suggested by several investigators for a number of regions of the nervous system of several different species.[18]

The correspondence between the distribution of acetylcholinesterase and levels of probable extensive arborization of the plexuses suggests further that the enzyme may be localized at the surfaces of the conducting and transmitting structures, since the greater the subdivision of axons and dendrites into finer and finer terminals, the greater the relative surface they present per unit mass and, in all probability, the larger the number of synaptic junctions. This has already been suggested for the somatosensory isocortex of the rat [2b] and, as in the latter case, would be consistent with the known localization of this enzyme in the sheath of the squid giant axon [19] and at levels rich in synapses in the bovine retina.[20]

No attempt will be made to correlate in detail the distribution pattern of acetylcholinesterase with the exact composition of the plexuses, since information about many fundamental aspects of the latter is lacking. The consistent peak of activity in Layer I can perhaps be attributed to terminal bushels of the dendritic shafts of pyramidal and spindle cells from all lower layers and to axons of Cajal horizontal cells. The peak at the rather ill-defined junction of Layers II and III may be associated with the axonal plexus consisting partly of arborizations of association afferent fibers whose horizontal myelinated segments form the line of Kaes-Bechterew. In postcentral isocortex, the zone of high acetylcholinesterase activity in Layer IIIb was correlated in part with the unmyelinated telodendra of the specific thalamic afferent fibers, but even the level at which such afferent fibers end in frontal cortex is unknown. The somewhat more superficial level of the zone of high enzyme activity in Layer III might be consistent with the suggestion of Ramón y Cajal,[21] based on Golgi impregnations of the motor area, that the specific afferent fibers end at a higher level in all frontal lobe cortex. This, however, has been denied by von Bonin [22] for fields rostral to and including Brodmann's area 44 on the basis that in these areas, as in postcentral isocortex, the external line of Baillarger is exclusively in Layer IV (redrawn slightly to include Layer IIIc of most authors). Weigert-Pal preparations of portions of the biopsy specimens used in our experi-

18. Hard, W. L., and Peterson, A. C.: The Distribution of Choline Esterase in Nerve Tissue of the Dog. Anat. Rec. **108**:57, 1950. Hard, W. L.; Peterson, A. C., and Fox, M. D.: Histochemical and Quantitative Studies on Choline Esterase Distribution in Cervical Sympathetic Ganglia, J. Neuropath. & Exper. Neurol. **10**:48, 1951. Koelle, G. B.: Histochemical Differentiation of Types of Cholinesterases and Their Localizations in Tissues of the Cat, J. Pharmacol. & Exper. Therap. **100**:158, 1950; Elimination of Enzymatic Diffusion Artifacts in the Histochemical Localization of Cholinesterases and a Survey of Their Cellular Distributions, ibid. **103**:153, 1951. Sinden, J. A., and Scharrer, E.: Distribution of Certain Enzymes in the Brain of the Pigeon, Proc. Soc. Exper. Biol. & Med. **72**:60, 1949.

19. Boell, E. J., and Nachmansohn, D.: Localization of Choline Esterase in Nerve Fibres, Science **92**:513, 1940.

20. Anfinsen, C. B.: Distribution of Cholinesterase in the Bovine Retina, J. Biol. Chem. **152**:267, 1944.

21. Ramón y Cajal, S.: Histolgie du système nerveux de l'homme et des vertébrés, Paris, A. Maloine, Vol. 2, 1911.

22. von Bonin, G.: Architecture of the Precentral Mortor Cortex and Some Adjacent Areas, in Bucy, P. C., Editor: The Precentral Motor Cortex, Ed. 2, Urbana, Ill., University of Illinois Press, 1949, Chap. 2, pp. 7-82.

ments also show the outer line of Baillarger in Layer IV and the deepest portion of Layer III. The peak of acetylcholinesterase activity in Layer V may correspond with the arborizations of axons of supragranular pyramidal and stellate cells occurring in relation to the protoplasmic plexus generated by the large pyramids of this layer, and perhaps to telodendra of association afferent fibers having their myelinated portions in the slightly deeper internal line of Baillarger.

Further speculations concerning these questions are not in order until the fine structure of frontal cortex is adequately studied in Golgi and Golgi-Cox preparations of suitable material. Meanwhile, it seems fair to suggest that in this region acetylcholinesterase is primarily associated with the neuropil and that its distribution is consistent with the supposition that it is localized at the surfaces of the axons, including synaptic junctions, and probably at the surfaces of the dendrites as well.[23]

Relationship of Cortical Acetylcholinesterase to Clinical Diagnoses.—The intracortical distribution pattern of acetylcholinesterase, as discussed in the previous section, did not show important differences in any of the biopsy specimens from the various clinical psychiatric categories represented. The curious feature of these experiments was, rather, the remarkable scatters of the acetylcholinesterase activities of the individual biopsy specimens, as revealed by the averages for the values for all the samples obtained from a given specimen (Table 2). The range is from 0.8 to 3.3 $\times$ 10^{-2} cu. mm. of 0.05 N HCl per microgram of dry weight, a more than fourfold difference, and almost three times the range such values show for rat cerebral cortex.[24]

When such mean values for each biopsy specimen are compared with the corresponding clinical diagnoses, the correlations, as shown in Table 3, seem to bring

23. These suggestions would not accord with the conclusions of Bok (Bok, S. T.: A Quantitative Analysis of the Structure of the Cerebral Cortex, Verhandl. k. Akad. van Wetensch., Amsterdam **35**:1, 1936), based on quantitative measurements in fixed and stained preparations, that per unit volume of human temporal lobe cortex the mass of neuronal perikarya and the total lengths of both axons and dendrites are essentially constant at all levels. The question of the validity of Bok's measurements and reasoning is complex, but certain biochemical data are not inconsistent with his conclusions concerning the cell bodies and will be discussed in detail in a future communication. For the fiber measurements drawings of the neuropil in Bielschowsky silver preparations were used; it is questionable whether these gave a complete picture, especially of the finest axonal and dendritic filaments. It is to be noted that a greater total fiber length was found in Layer V. No estimations of fibrillar or protoplasmic surface areas or of the numbers of synapses or dendritic spines were possible. Moreover, the clearly different proportions of cortical mass occupied by large-caliber myelinated axons and by blood vessels, together with the relative constancy of neuroglial elements at different cortical levels, make it hard to believe that nerve cell bodies and the finer elements of the neuropil furnish the same contribution to the tissue mass at all levels.

An even more serious difficulty with this suggestion is the possibility recently pointed out to one of us (A. P.) by Dr. David Nachmansohn that, by analogy with different gross subdivisions of the central and peripheral nervous systems, the acetylcholinesterase activity might vary considerably in the many different cell types and different afferent fibers that make up the cortical plexuses. If this were so, even tentative conclusions of the sort made herewith would be impossible in the present state of knowledge.

24. Experiments now in progress indicate that the range of average acetylcholinesterase values in human cortex exceeds that for at least two other enzymes that are being studied by similar ultramicroquantitative methods—alanylglycine dipeptidase and cytochrome oxidase.

out two other curious features. First, the range of activities was greater (0.9 to 3.3 $\times$ 10^{-2} cu. mm. per microgram) among the 12 biopsy specimens obtained from psychotic patients than it was (0.8 to 1.8 $\times$ 10^{-2} cu. mm. per microgram) among 5 specimens from patients considered not to be psychotic (persons with psychoneuroses or intractable pain). Second, all the specimens having the highest overall acetylcholinesterase activities were from among the psychotic patients. From this group, 7 of 12 specimens showed mean acetylcholinesterase activities higher than the mean activities shown by any of the 5 specimens from nonpsychotic patients. Of the seven patients with high cortical acetylcholinesterase activities, all but one (H. S., a patient with a diagnosis of paranoia) were from among the group of deteriorated schizophrenic patients, although one of these (A. J.) was

TABLE 3.—*Correlation of Mean Cortical Acetylcholinesterase Activities per Specimen and Clinical Diagnoses*

Group	Diagnosis	Patient	Acetylcholinesterase (Average Cu. Mm. 0.05 N HCl per Microgram × 100)
Nonpsychotic	Intractable pain (cancer)	*R. L.	1.8
		C. S.	1.5
	Psychoneurosis		
	Obsessive-compulsive	*M. K.	1.3
		*V. R.	1.4
	Conversion hysteria	*E. C.	0.8
Psychotic	Schizophrenia		
	Paranoid	K. McL.	1.4
	Hebephrenic	*D. A.	2.6
	Catatonic	A. J.	2.8
		*E. V.	2.9
		R. M.	2.1
		*J. K.	1.4
		*G. F.	1.7
		A. T.	0.9
	Other types	H. C.	3.3
		*R. E.	2.2
	Paranoid condition	H. S.	3.0
	Manic-depressive		
	Manic	E. M.	1.3

* Patients belonging to "selected" nopsychotic and psychotic subgroups (see text and table 1).

somewhat older than the rest and her psychosis had developed at a relatively advanced age. The other five psychotic patients showed cortical acetylcholinesterase activities within the same range as those shown by patients who were not psychotic. They included three deteriorated catatonic patients, one paranoid schizophrenic patient in relatively good contact, and one manic patient in a hypomanic state at the time of operation.

In the case of specimens obtained from patients belonging to the "selected," contrasting subgroups, as defined in the clinical part, acetylcholinesterase activity showed somewhat more variability in the cortex of deeply psychotic patients (range 1.4 to 2.9 $\times$ 10^{-2} cu. mm. per microgram) than in the cortex of nonpsychotic patients (0.8 to 1.8 $\times$ 10^{-2} cu. mm. per microgram). Three of five specimens from the psychotic group had a higher activity than was found in any of the others.

All these results are summarized graphically in Figure 3, which shows the wide scatter in the mean acetylcholinesterase activities per biopsy specimen, and which

indicates that, whether these experiments are viewed as a whole or on the basis of selection of clear-cut extremes with respect to clinical behavior, the frontal cortex of some patients with long-standing psychoses had an unusual degree of acetylcholinesterase activity. For all cases, the mean activity among the 5 nonpsychotic patients was, in cubic millimeters per microgram, $1.4 \pm$ S.E. 0.17×10^{-2}, and among the 12 psychotic patients, $2.1 \pm$ S. E. 0.23×10^{-2}. For the selected patients, the mean among the four nonpsychotic patients was $1.3 \pm$ S. E. 0.21×10^{-2}, as compared with a mean of $2.2 \pm$ S. E. 0.28×10^{-2} for the five profoundly psychotic subjects. The higher range of activities among all psychotic patients than among all nonpsychotic patients was not statistically significant ($P > 0.05$) according to Fisher's

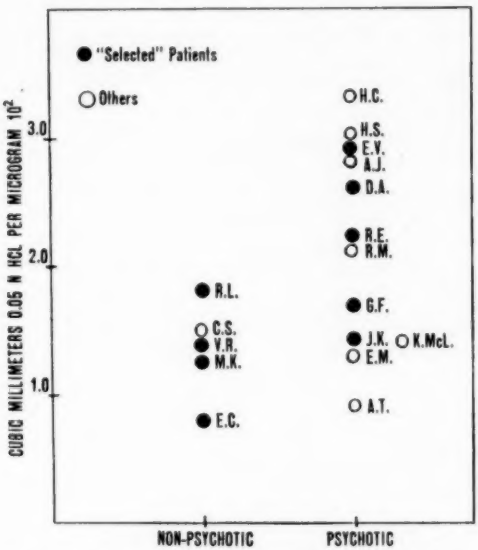

Fig. 3.—Scattergrams showing mean cortical acetylcholinesterase activity of each individual biopsy specimen according to groups and subgroups of patients studied.

t test for small samples.[25] However, in a comparison of the selected psychotic and the selected nonpsychotic subjects, such elevation in range of values was at the borderline of significance ($P = 0.05$). This could be of interest in view of the fact that the selective process seemed to provide populations that clinically were different with respect to severity of behavior disorder and degree of personality disintegration. There are, however, a number of other factors of possible importance that must be considered in relation to these findings.

There was no apparent correlation between averaged acetylcholinesterase activities in the given specimens and either the age or the sex of the patient. At first sight, it appeared that the dose of thiopental (pentothal®) sodium might have

25. Fisher, R. A.: Statistical Methods for Research Workers, Ed. 10, Edinburgh, Oliver & Boyd, Ltd., 1946.

influenced the results. Three of the patients (H. S., A. J., and E. V.), with the highest over-all cortical acetylcholinesterase activities, were operated on with the use of local anesthesia only, and another patient (R. M.), who had the least thiopental of those receiving the drug, also showed a relatively high activity. On the other hand, the patient (H. C.) whose cortex had the highest activity of them all also received the most thiopental, and one patient (G. F.), lobotomized with use of local anesthesia, showed relatively little cortical acetylcholinesterase. Moreover, the cortices of rats killed by excessive doses of thiopental sodium have shown no loss of acetylcholinesterase activity, and, as noted in the section on methods, assay of this enzyme is done in the presence of a barbiturate buffer. It is unlikely, therefore, that the thiopental in the specimen had an important influence, but this does not answer the serious problem presented by possible unknown effects of chronic drug administration upon brain enzymes. Some of these patients may have received medication of various sorts over considerable periods. This was certainly true of the patients with intractable pain. The possible effects of chronic drug intake upon cerebral acetylcholinesterase are unknown, and this constituted, therefore, an unknown and uncontrolled factor in these experiments.[26]

It is even more difficult to assess the possible influence of previous convulsion therapy upon cortical acetylcholinesterase. As might be expected, the patients who were deeply psychotic were just those who, on the whole, had received the most shock therapy, and since these were the patients among whom cortical acetylcholinesterase activity was sometimes elevated, the treatment cannot be excluded as having brought about this change. Again, as one might anticipate, very little convulsion therapy had been administered to patients in the relatively normal pain-psychoneurosis category, although the patient with hysteria (E. C.) had had 19 electric shocks in the year before operation. If the whole series is arbitrarily divided into a high and a low group according to whether the average acetylcholinesterase was above or below 2.0×10^{-2} cu. mm. per microgram, then, with one exception, all the patients who had had no shock therapy were in the low group. Furthermore, both the patients (H. S. and R. M.) who had been given significant amounts of electric shock (60 and 71 treatments, respectively), as well as both those (H. C. and E. V.) who had had pentylenetetrazole- (metrazol®)-induced convulsions, were in the high group. On the other hand, one patient (A. J.[27]) who received no shock treatment of any sort was in the high group, and the rest of those who had been treated either with electric shock or with insulin were about evenly divided between the two groups. It is impossible therefore to exclude previous shock therapy as a cause of the high cortical acetylcholinesterase in some of these patients, but equally difficult to be sure that it was the cause. Obviously, it is a problem that should be studied under adequately controlled conditions, especially since acetylcholinesterase activity does appear to increase in cortical lesions that are the site of epileptiform electrical discharges and the point of origin

26. Schütz (Schütz, F.: The Effect of Barbiturates on Cholinesterase in Different Tissues, J. Physiol. **102**:269, 1943) has shown that in guinea pigs prolonged treatment with barbiturates produces a lowering of muscle and spinal cord, but not of brain, cholinesterase. No such changes occurred after a single deep narcosis with these agents.

27. This, however, was the somewhat older patient (aged 61), who, in addition, showed certain cortical histopathological changes, as will be noted below.

of focal cortical seizures.[28] However, even though the enzyme activity were enhanced during, and for a period after, a course of treatment that produced cerebral seizures, it would be remarkable if such a change persisted for long after cessation of treatment. If convulsion therapy were postulated to be the cause of the higher cortical acetylcholinesterase activity in some of these patients, it would be necessary to assume that the change did so persist for variable periods up to as long as 10 years in the case of two of them (D. A. and E. V.). It is necessary to state that the possible effect of previous shock therapy of various types was another inadequately controlled factor in this series of experiments.

The neuropathological findings will be discussed next. With few exceptions, the specimens were considered to be within normal limits on the basis of the four neurohistological stains for neurones and neuroglia that were routinely employed. Many of these specimens exhibited minor neuronal changes of the sort so often described as characteristic for the cortex in schizophrenia, but which critical observers have found to be inconstant and nonspecific, and often presumably the result of artifact.[29] In the Nissl preparations such changes included occasional swollen and vacuolated nerve cells or others showing cell sclerosis and, in Cajal silver stains, increased argyrophilia. Intraneural lipochrome deposits were common even in the younger patients, and considerable intracellular sudanophilic lipid was often demonstrable. Occasionally, in the Cajal gold preparations, somewhat hypertrophied astrocytes containing definite fibers were found in the cortical gray matter. Four patients (A. J., E. V., R. L., and A. T.) showed a significant degree of acute swelling of the oligodendroglia both in the cortex and in the subcortical white matter. Two others (R. E. and C. S.) showed minimal, but definite, oligodendroglial swelling in the white matter only.

In two of the patients with catatonic schizophrenia (A. J. and A. T.) sufficient cortical abnormality was found to warrant placing them outside the range of normal limits. The cortex of A. J. (a woman aged 61) contained unusual numbers of swollen and vacuolated nerve cells, especially in Layers II, III, and IV. There were definite microscopic plaques in the silver preparation for neurofibrils, and the glial stains showed, in addition to oligodendroglial swelling, both hypertrophied, partially activated-appearing microglia cells and definite intracortical nodules made up of fibrous astrocytes. In the cortex of A. T. (a man aged 20) no neuronal changes were certain except, perhaps, for some sparsity in the cell population in Layers V and VI, but there was definite thickening of the pia-arachnoid, and the swelling of the oligodendroglia was very marked, both in the gray and in the white matter.

It is difficult to evaluate the significance of any of these changes or to estimate the possible importance in their production of hospitalization, previous convulsion therapy, or other factors incident to chronic mental disease. The significance of acute swelling of the oligodendroglia will be discussed in detail elsewhere, but it should be noted that of the 17 patients under consideration, only 6 showed this phenomenon,

28. Pope, A.; Morris, A. A.; Jasper, H.; Elliott, K. A. C., and Penfield, W.: Histochemical and Action Potential Studies on Epileptogenic Areas of Cerebral Cortex in Man and the Monkey, A. Res. Nerv. & Ment. Dis., Proc. **26**:218, 1946.

29. Wolf, A., and Cowen, D.: Pathology, in Mettler, F. A., Editor: Selective Partial Ablation of the Frontal Cortex, New York, Paul B. Hoeber, Inc., 1949, Chap. 27, pp. 453-472.

and that these included 4 of the patients with chronic schizophrenia and the 2 with intractable pain. There did not appear to be any definite correlation among these specimens between either oligodendroglial swelling or any other of the histopathological changes noted and the level of acetylcholinesterase activity.

Finally, the clinical nature of the population of patients who showed a relatively high cortical acetylcholinesterase activity must be viewed critically. At first sight, the data of Tables 1 and 2 seem to suggest that this phenomenon was peculiar to patients with chronic deteriorated schizophrenia, and, as a first approximation, the "selected" nonpsychotic and profoundly psychotic patients did form contrasting and relatively homogeneous populations. Closer inspection, however, brings out inconsistencies even in the selected groups, and many more if the rest of the patients are also considered. Two of the patients (J. K. and G. F.), who most perfectly satisfied the criteria for placement in the category of those exhibiting profound withdrawal and dilapidation showed cortical acetylcholinesterase values right in the normal range. It is of interest that one of these patients (J. K.) had had no shock therapy whatsoever and the other (G. F.) only two electric shocks two years before operation. The patient, A. T., although ill for a relatively short time, otherwise also fulfilled these criteria quite perfectly; yet his cortical acetylcholinesterase activity was next to the lowest in the whole series of 17 patients. On the other hand, patient H. C., whose acetylcholinesterase activity was the highest observed, had originally received the diagnosis of paranoid schizophrenia and had required continuous hospitalization for only three years. The most serious inconsistency of all is due to patient H. S., whose cortical acetylcholinesterase activity was higher than that of any of the others except H. C. Clinically, he was not thought to be schizophrenic and was classified as having paranoid condition. He was deluded in the political sphere only, showed appropriate affect, and was in good contact at the time of operation. It has already been noted that this patient had received 60 electric shocks during the year prior to lobotomy.

The only logical inferences to be drawn from these results are that human frontal isocortex shows astonishing variability in its capacity to hydrolyze acetylcholine and that this is especially so in persons with chronic schizophrenia. There follows, in spite of serious inconsistencies and of many clinical factors difficult to control in patients of the sort studied, the suggestion that, whatever may be the reason, in some persons with long-standing and progressive schizophrenic withdrawal, this cortical acetylcholinesterase activity is greater than in persons whose contact and personality structures are relatively well preserved. This can be only a suggestion because of the small number observations and the many difficulties in interpretation that have been discussed. Its meaning, even if substantiated by more and better controlled experiments, is obscure.

If the measured activity of an enzyme in a given sample of tissue is related to the actual, as well as the potential, turnover rate of the metabolic system of which it is part, then the variability in over-all acetylcholinesterase activity shown by these specimens should reflect differences in the usual rates of acetylcholine turnover in them. The higher potential rate of hydrolysis of this compound in some would suggest a higher normal rate of acetylcholine metabolism. If this substance is indeed one with a role of critical importance in the physical chemistry of nerve action, the further suggestion can be made that in those specimens exhibiting

relatively high cortical acetylcholinesterase activity there had been a chronic increase in rate of neuronal discharge. Such a suggestion has already been made for epileptogenic cortical foci,[28] but in this case there was corresponding electroencephalographic evidence for continuous hyperactivity of the cortical cells, and analogous changes have not often been observed in the electrocorticograms of psychotic subjects. However, a few observations not inconsistent with such an hypothesis have been reported. In frontal cortical biopsy specimens of schizophrenic patients the large ganglion cells show protein and nucleoprotein depletion of the sort accompanying exhaustive discharge of neurones.[30] In one study[31] acetylcholine was reported as present in the cerebrospinal fluid of some psychotic subjects, particularly catatonic persons, although this was not observed in another.[32] Finally, there is the suggestive observation that certain schizophrenic patients are unusually resistant to the electroencephalographic changes ordinarily brought about by chronic administration of the acetylcholinesterase inhibitor diisopropyl fluorophosphate.[33]

These experimental results are so highly provisional that it is scarcely necessary to emphasize that physiological changes of any sort found in chronically psychotic persons, however well established, are rather more likely to be the result of long-continuing mental illness than of significance in its etiology. In general, patients with schizophrenia show abnormally great variability with respect to almost all measurable physiological and biochemical elements, and it is likely that cortical acetylcholinesterase activity is no exception. In all such matters it is difficult to determine the respective roles of the illness itself, together with its own secondary somatic manifestations, and factors such as lengthy hospitalization, relative inaction, an often inadequate diet, sometimes prolonged use of drugs, and receipt of varying amounts of convulsive therapy. Physical or chemical changes in the brains of patients with chronic schizophrenia cannot be regarded as related to the genesis of the psychosis until conclusively established in patients exhibiting the earliest manifestations of their illness. In this connection, it should be pointed out again that in this series the only patient (A. T.) whose disease was of relatively short duration showed not a high cortical acetylcholinesterase activity, but the next to the lowest observed. In patients of the sort represented in this study not even the most thoroughly established neurophysical or neurochemical changes should ever be considered as necessarily having an important relation to the etiology of schizophrenia.

The results of these experiments demand confirmation or rejection based on a more definitive study, more fully controlled with respect to various aspects of physiological and psychological status and other clinical variables. If cortical

30. Hydén, H., and Hartelius, H.: Stimulation of the Nucleoprotein Production in the Nerve Cells by Malononitrile and Its Effect on Psychic Functions in Mental Disorders, Acta psychiat. et neurol., Supp. 48, p. 1, 1948.

31. Alcober Coloma, T.: Acetylcholine in the Cerebrospinal Fluid of Mental Patients, Trab. inst. nac. cienc. med. **3**:359, 1943-1944.

32. Tower, D. B., and McEachern, D.: Acetylcholine and Neuronal Activity: I. Cholinesterase Patterns and Acetylcholine in the Cerebrospinal Fluids of Patients with Craniocerebral Trauma, Canad. J. Res. **27**:105, 1949.

33. Rowntree, D. W.; Nevins, S., and Wilson, A.: Effects of DFP in Schizophrenia and Manic-Depressive Psychosis, J. Neurol., Neurosurg. & Psychiat. **13**:47, 1950.

acetylcholinesterase activity does show wide variability in human patients, it is important to know whether or not this is a specific enzymatic alteration or is, perhaps, accompanied by parallel changes in other important intracellular enzymes. Experiments are now in progress designed to answer as many as possible of these questions.

SUMMARY

The quantitative cytoarchitectonic distribution of acetylcholinesterase has been determined in 17 biopsy specimens of human frontal isocortex obtained during lobotomy for mental illness or intractable pain.

The cytoarchitectonic distribution of acetylcholinesterase was essentially constant. Activity was relatively great in cytoarchitectonic Layer I, the II-IIIa junction, and the midzones of Layers III and V. The intracortical distribution of this enzyme indicates that it is primarily associated with the neuropil and suggests its localization at the surfaces of conducting structures and synapses.

The mean acetylcholinesterase activity for a given specimen showed great variability, more so among psychotic than nonpsychotic patients (persons lobotomized for psychoneurosis or intractable pain). The mean activity was increased in 7 of 12 psychotic patients, as compared with 5 nonpsychotic patients. In comparable, but contrasting, subgroups the range of such cortical acetylcholinesterase activities was higher among five patients with chronic deteriorated schizophrenia than among four patients with psychoneurosis or intractable pain. The possible meaning of these results and their relation to clinical status, medication and anesthesia, previous convulsion therapy, and various histopathological findings are discussed.

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NATURE AND TREATMENT OF TICS IN ADULTS

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FEW PEOPLE consult the psychiatrist because of tics. The neurologist is asked to examine only the severest, most bizarre and incapacitating forms. Yet the symptom is seen frequently. Many psychoneurotic patients display tics in the form of automatic gestures, grimaces, twitches, jerks, and spasms, for which they do not primarily seek help. For this reason, the psychiatrist is probably most able to contribute to an understanding of tics, since, in the vis-á-vis position, he can observe periodic outbursts of tics in association with psychological problems. In many instances, the discussion of certain conflicts during the interview is accompanied by an obbligato of tics, which seem to underscore the patient's anxiety.

In this paper, several cases of psychoneurosis in which tic was a leading symptom will be reported. Most previous studies of tics have been on children; all our patients were adults. In all instances the tic originally appeared to be completely adventitious. However, when the ego structure and the psychodynamics of the patient were understood, the meaning of the tic became clear. In addition, it was possible to alleviate the symptom through special techniques of psychotherapy. The treatment of these patients disclosed the close relationship between tics and obsessional neurosis.

DEFINITION, DESCRIPTION, AND CLASSIFICATION

Tics most frequently appear during late childhood or early adolescence. They consist of abrupt movements of muscle groups which are usually associated with some purposeful action. For example, as a result of a foreign body, the eyes may blink. In this case the orbicularis oculi muscles contract in response to a sensory stimulus to the cornea or conjunctiva. Sometimes identical muscle movements may occur in which no external stimulus is evident. It is inferred that subjective factors are operating to induce the blepharospasm and that the movements are no less purposeful.

Tics characteristically involve closely associated muscle groups which normally participate in integrated movements or carry out a common function. The muscles of the face, head, and neck are an example. Although each receives a separate innervation, they frequently react together for a common purpose. Another distinctive feature of the tic is its relative irresistibility. The afflicted person is aware of increasing tension within himself, which is concentrated in certain muscles. Although he may try to ignore the unpleasant feelings, the tension becomes unbearable. Finally, when he can desist no longer, he allows the muscles to contract and perform special motions in order to relieve the intolerable tension.

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Tics are manifested in endless variety. The eyes blink; the shoulders hunch; the head twists; the teeth are bared; the arms are flung; the fingers clench; the nose wrinkles; the tongue protrudes, or any other movement may occur which can become endowed with meaning. One patient contracted his anal sphincter in a tic-like fashion. However, the primary site of manifestation is the head and neck, and the secondary site, the extremities.

The patient can sometimes inhibit the tic movements by an act of will, absorption in study, conversation, or other distracting activity; but such inhibition is temporary. Tics are less apt to occur during periods of emotional tranquility, but episodes in which the patient is under stress may be accompanied by a storm of grimaces and jerks.

These are, then, the three characteristic features of the tic: (1) its occurrence in functionally related groups of muscles; (2) its association with an irresistible tension, which is relieved only by performance, and with anguish should the urge to act be denied, and (3) its partial control by the will.

CLASSIFICATION AND THEORIES OF DEVELOPMENT

Tics have been classified in various ways, depending on the special bias of the investigator. A phenomenological classification of tics on the basis of their location, such as the face, eyes, trunk, or extremities, or of the type of movement is valuable only as it indicates the variability of the different forms of expression of the tic. The distinction between "organic" and "psychogenic" tics has no justification. Adventitious movements following epidemic encephalitis have been described as "tics."[1] The question may be raised whether these "organic tics" are the result of damaged neural connections or the expression of an impaired personality,[2] and, hence, as "psychogenic" as tics arising without evident disease of the nervous system.

Classification of tics on a psychological basis presupposes a theory of pathogenesis and a notion of the function that a tic serves. If the tic is regarded as a psychoneurotic motor phenomenon, one must then distinguish between primary tics and secondary tics. The former represent a discharge of aggressive or erotic feelings in the presence of an impaired or inadequately developed ego. Such movements are extremely common among young school children, according to Blatz and Ringland,[3] and come about through either overstimulation or excessive restriction of the spontaneous motor activity of the growing child. Primary tics do not represent a psychoneurotic symptom, but, rather, are the resultant of a conflict between the child's urges and the requirements of the environment. With increased adaptability and the acquisition of other methods of mastering tension, the movements usually disappear during childhood. However, when excessive restriction or overexcitation persists, a fixed tic may develop.[4] The secondary tics consist of motor phenomena which the ego employs as defensive measures against the feelings which it is

1. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944, p. 424.

2. Schilder, P.: The Organic Background of Obsessions and Compulsions, Am. J. Psychiat. **94**:1397, 1938.

3. Blatz, W., and Ringland, M.: Study of Tics in Preschool Children, Toronto, University of Toronto Press, 1935.

4. Levy, D. M.: On the Problem of Movement Restraint: Tics, Stereotyped Movements, Hyperactivity, Am. J. Orthopsychiat. **45**:644, 1944.

impelled to express. Tics, as seen by the clinician, usually are of the secondary type, namely, fusions of impulse and defense.

In 1907, Meige and Feindel [5] published their classic monograph, "Tics and Their Treatment." They characterized the tic as . . .

> a coordinated, purposive act, provoked in the first instance by some external cause or by an idea; repetition leads to its becoming habitual, and finally to its involuntary reproduction without cause and for no purpose, at the same time as its form, intensity and frequency are exaggerated. It thus assumes the characters of a convulsive movement, inopportune and excessive; its execution is often preceded by an irresistible impulse, its suppression associated with malaise. The effect of distraction or of volitional effort is to diminish its activity; in sleep it disappears. It occurs in predisposed individuals who usually show other indications of mental instability.[6]

This statement epitomizes all the clinical features of the tic movement for which any theory of pathogenesis must account.

In the early years of this century, many neurologists recognized that tics were somewhat under the influence of voluntary control. For this reason, Meige and Feindel believed that "defective will power" was responsible for the perpetuation of the tic movements. Patients with tic were considered to be "superior degenerates, mentally infantile, childish, unstable and inconstant. . . ." The tic was regarded as closely analogous to the obsessional thought or act, because in both an irresistible sensation was associated with intolerable anxiety or distress which could be relieved only by an appropriate performance. Charcot had asserted that "tics of the mind may be manifested in tics of the body." Tics, to Meige and Feindel, are never random movements, but always systematic, purposeful acts for which reasons could be found.[7] The precipitating stimulus for a tic is either an external trauma or a psychological event. When this stimulus occurs to a predisposed person, the tic persists. Subsequently, in some fashion, the association with the original event is lost.

Brain [8] understood the tic as a conditioned reflex, a motor response which has become associated with an inappropriate stimulus. However, he extended his view by recognizing that a tic has psychological significance as a defense against the circumstances which elicited it, and, by implication, as a defensive gesture designed to master certain emotional states.

The problem of tics was also studied by several early psychoanalysts. Clark [9] interpreted tics as symbolic erotic acts but did not note their defensive function. Abraham [10] believed that the tic was a pregenital conversion symptom, with an anal-sadistic type of object relationship. In this way, he noted a psychodynamic similarity between tics and the obsessional neurosis. He differentiated tics and compulsive acts by asserting that the patient with the tic does not recognize the importance of the symptom in his mental life, while the obsessional patient fears disaster if he omits his ritual. The patient with tic experiences discomfort if he does not perform the tic, but the obsessional patient experiences anxiety when he desists from his ritual.

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5. Meige, H., and Feindel, E.: Tics and Their Treatment, London, S. Appleton, 1907.
6. Meige and Feindel,[5] pp. 260-261.
7. Meige and Feindel,[5] p. 49.
8. Brain, W. R.: The Treatment of Tic (Habit Spasm), Lancet **1**:1295-1296 (June 23) 1928.
9. Clark, L. P.: Remarks on Mental Infantilism in the Tic Neurosis, M. Rec. New York **85**:553 (March 28) 1914.
10. Abraham, K.: Contribution to a Discussion on Tic, in Selected Papers, London, Hogarth Press, 1950.

Ferenczi [11] emphasized the heightened narcissism of patients with tic who react to apparently minor stimuli as though the whole ego had been assaulted. The narcissism is not so marked in obsessional patients, he believed, because compulsive rituals consist of real actions which alter the external world rather than discharge instinctual tension. Klein [12] concurred in Ferenczi's conclusions that the tic represents, in some cases, a masturbatory equivalent, but she rejected the notion that it is a primary narcissistic symptom related to the psychoses. In a detailed case study, she discovered genital, oral, and anal impulses which were discharged in the tic symptom. The tic appeared when homosexual and masturbatory impulses were repressed. In this way, the symptom represented a substitute gratification and a partial sublimation.

The early psychoanalytic studies of tic emphasized the instinctual aspects of the symptom rather than its defensive or adaptive function. Solomon [13] rejected the psychoanalytic formulations of his contemporary Clark, although he admitted that the cause of tic is usually unconscious. Solomon proposed an "evolutionary" theory of tics. According to this hypothesis, the psychophysical organism develops through a process of progression, fixation, and regression. Tics represent regressive methods of response to certain irritations or ideas and are essentially adaptive in nature. In the nervous system which has defective patterns of adaptation tics are liable to develop as a regressive dissociation from other defensive activities. Solomon's views presaged certain current theories of the regressive effect of stress on psychological and physiological function.

Only in recent years, with the development of ego psychology, has the defensive function of the tic on a psychodynamic basis been elucidated. Gerard [14] reported four cases in which the tic served as a defense mechanism. In all her cases the tic was an appropriate response to an overwhelming traumatic experience. Prior to the critical event, however, each child was aggression-inhibited, suffering from either an immature ego or an excess of instinctual tension. Fixation in the form of tic occurred at the point where the synthetic function of the ego broke down.

Within the past decade, Margaret Mahler and her co-workers [15] have investigated tics from the point of view of both analytic findings and developmental understanding. She noted that motility is a prominent source of pleasure for the growing

11. Ferenczi, S.: Psychoanalytic Observations on Tic, in Further Contributions to the Theory and Technique of Psychoanalysis, translated from the German by J. T. Suttle and others, London, L. & V. Wolf, 1926, p. 142.

12. Klein, M.: A Contribution to the Psychogenesis of Tics, in Contributions to Psychoanalysis, Hogarth Press, London, 1948, p. 117.

13. Solomon, M.: Tics, Interstate M. J. **22**:41, 1915; On the Genesis and Meaning of Tics, J. Abnormal Psychol. **10**:329, 1915-1916; Freudian Theory of the Pathogenesis of Tics, Chicago M. Rec. **36**:589, 1914.

14. Gerard, M.: The Psychogenic Tic in Ego Development, in Freud, A., and others, Editors: Psychoanalytic Study of the Child, New York, International Universities Press, Inc., 1946, Vol. 2, p. 133.

15. (*a*) Mahler, M. S., and Rangell, L.: A Psychosomatic Study of Maladie des Tics, Psychiat. Quart. **17**:579, 1943. (*b*) Mahler, M. S.: Tics and Impulsions in Children: A Study of Motility, Psychoanalyt. Quart. **13**:430, 1944. (c) Mahler, M. S.; Luke, J. A., and Daltroff, W.: Clinical and Follow-up Study of the Tic Syndrome in Children, Am. J. Orthopsychiat. **15**:631, 1945. (*d*) Mahles, M. S., and Luke, J. A.: Outcome of the Tic Syndrome, J. Nerv. & Ment. Dis. **103**:433, 1946.

child, and hence is an avenue for instinctual discharge. The child who acquires a tic usually passes through an initial phase of hyperkinesis. This is determined both by a constitutional increase in the need for motor activity and by excessive restriction and overstimulation. One indication of the "pre-tic" stage is temper tantrums, which occurred in 80% of her patients with the tic syndrome. In crystallized tics, the active aggressive impulses and passive tendencies fuse, so that the symptom represents, according to Mahler, both provocative erotic aggression toward the parents in the gestural ideomotor vocal sphere and the defense against them as aggressors. The tic symbolizes the child's experience of being overwhelmed by an impulse and the defensive innervation against it.

Mahler classified tics into three types: (1) tics resulting from overtaxed affective motility and the claim for control; (2) tics which develop later, when an increase of instinctual tension is met with the threat of punishment for autoerotic activities, and (3) tics in adolescents and adults, which are symbolizations in terms of muscle groups, due to hypercathexis of the organ of motility. Patients with the first type of tic characteristically demonstrate restless activity, and the movements are transient and variable in form and frequency. In the second kind of tic there is typical motor inhibition with "nervous habits," rather than the unabiding restlessness of the first type. The "fixed tic" of the older patient has undergone a process of isolation from the ego, and the psychodynamic components are similar to those occurring with the traumatic neuroses. In Mahler's experience, these tics are the most difficult form to reach with psychotherapy. The "fixed tic" corresponds to the "adult tic" discussed in her paper as "secondary, psychogenic tic."

Fenichel [16] synthesized much of the preceding psychoanalytic investigations. He regarded tics as repressed movements which return against the ego. The tic has three components: (1) a part of the original affective syndrome; (2) a defense against the affect, and (3) motor impulses that were once associated with the repressed emotion. He regarded the patient with tic as possessing a compulsive narcissism. Moreover, the muscle movements not only may be mimetic revivals of a repressed conflict, but actually may represent introjected objects or infantile relationships.

REPORT OF CASES

CASE 1.—*Tics of the mouth and flexion spasms of the head and neck.*

This case will be reported in detail, since it illustrates most of the points of genesis and treatment.

A 43-year-old housewife presented temper tantrums, asthma, and stuttering in childhood. She was raised in an atmosphere of parental friction and divided loyalties. Speech, consisting of movements of the tongue and lips, as well as the use of words, became a means of expressing aggression and bringing reprisal upon herself. Her initial ambivalence toward both parents gradually extended to other people, and a profound fear of strangers developed. She reacted to the xenophobia by withdrawal from society and emotional isolation. Many obsessional rituals and moderately severe depressive episodes occurred, and she suffered for many years with an oppressive sense of guilt. At the age of 38 a tic of the lips appeared, consisting of pursing, sucking movements. Two years later flexion spasms of the head complicated the predicament, so that speech and social relationships, even with her family, became practically impossible.

Present Illness.—Five years before she sought psychiatric aid, the patient began to exhibit automatic puckering twitches of the lips, which gradually became severer and finally almost

16. Fenichel, O.: Psychoanalytic Theory of Neurosis, New York, W. W. Norton & Company, 1945, p. 317.

uncontrollable. If she was quietly preoccupied, her lips were calm. When she encountered strangers or participated in social functions, her efforts to speak were interrupted by a flurry of spasmodic twitches of the mouth. Shortly after the mouth tic began, a mass in the right breast was discovered. She underwent three operations before a radical mastectomy was finally performed. One year later she was sterilized by x-rays. Two years after the onset of the mouth tic an intolerable aching and drawing sensation of the neck muscles developed, followed by intermittent flexion spasms, during which her head pressed downward tightly against her chest. She was unable to move from this position, except with strenuous upward pressure against her chin. As a result of the two tics, movements of speaking and eating became practically impossible. As the symptoms became even more incapacitating, she was unable to eat with her family, and consequently most of her meals were taken alone. Each time speech was attempted, her head suddenly flexed, so that her face was hidden from the other person. Added to this, the twitches of her lips made whatever speech remained almost unintelligible. She acquired a technique of supporting her chin with her hand, and in this way was enabled to speak in a brief, fragmentary way.

At the time the tics reached climactic severity, there developed a depression which included feelings of anxiety, self-recrimination, insomnia, anorexia, and hypochondriacal preoccupation. The combination of all these symptoms resulted in complete seclusion for the patient for about two years prior to her beginning psychotherapy.

Past History.—At the age of 5 years the patient had asthma and urticaria, and for a few years she also stuttered. She was subject to temper tantrums as a child, but these disappeared in the preadolescent period. Although she did not recall sucking her thumb, all her life she derived great satisfaction and consolation from sucking. In fact, as an adult, when distressed, she would often retire to her bed with a bottle of milk fitted with a rubber nipple. When she was 17, she was found to have pulmonary tuberculosis and was confined to her home for a year.

Family and Marital Relationships.—Her father was a wealthy physician who had never practiced medicine. He was addicted to both alcohol and morphine. One of her most vivid recollections concerned the frightful transformation in character and appearance when her father was under the influence of these drugs. On occasion, he would suddenly appear behind her, and she would turn, scarcely recognizing the angry, disheveled creature, who had been a benign, cultured person a few hours earlier. In the father's lucid periods, he read considerably and had many interests. At such moments she would experience a feeling of warmth, companionship, and security, which she never found again. In later years she learned of his "wickedness," which was said to be homosexual attachment for young boys. When the patient was 5 years old, at about the time the asthma and urticaria developed, her father began to suffer with spasmodic torticollis, an ailment which persisted until his death, 28 years later.

Her mother was described as a beautiful woman, who had had many lovers. She was much younger than her husband and was pregnant with the patient's older sister when the marriage was performed. There was constant friction between the parents. The patient's loyalties were always being tested and divided. Both parents were capable of deep tenderness, as well as harsh, unreasoning vituperation. When the patient was 22, the parents finally separated.

Her older sister became alcoholic. In her later years, this was associated with psychotic behavior and convulsions. Rather than commit the sister to a mental hospital, the patient cared for her at home, watching her disintegrate into a helpless psychotic invalid. Six months before the spasms of head flexion began, the sister died, following a head injury sustained during a convulsion.

The patient was married, on only slight acquaintance, to a man she had met shortly after her parents separated. There was a mutually satisfactory sexual relationship, but otherwise they were unable to communicate with each other. Early in the marriage she decided that some matters belonged to him and others to her. There was no effort at mutual discussion or understanding—merely a division of labor and assignment of obligation within the family orbit. In addition, her husband had defective hearing and used an auditory aid, which he customarily detached in the evening at home, thus making communication even more difficult.

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The patient was married, on only slight acquaintance, to a man she had met shortly after her parents separated. There was a mutually satisfactory sexual relationship, but otherwise they were unable to communicate with each other. Early in the marriage she decided that some matters belonged to him and others to her. There was no effort at mutual discussion or understanding—merely a division of labor and assignment of obligation within the family orbit. In addition, her husband had defective hearing and used an auditory aid, which he customarily detached in the evening at home, thus making communication even more difficult.

Social Relationships.—The patient had been shy and diffident since early childhood. Because the family moved about a great deal, she never became established in any community and always felt herself to be an outsider. Violent quarrels between her parents made her afraid of both mother and father and increased her sense of isolation within the family circle.

The early temper tantrums which the patient displayed evolved into a habit of making sudden rude, tactless, or even cutting remarks. This outraged her mother, who reproached the patient by telling her that she had a "tongue like a viper." The patient was both frightened and impressed by this analogy and became intensely aware of her tongue, looking on it as an instrument to hurt people and as a means of alienating her from her mother. The fear of injuring someone with her tongue persisted into later life. After an evening with strangers, she would be troubled for days lest she had inadvertently offended someone by a chance remark. In the divided household of her childhood, it was imperative that she avoid speaking of certain topics. Father would be enraged at subjects she could readily discuss with mother, and mother would be equally furious whenever the patient talked with father. The split between mother-topics and father-topics was so sharp that at times the patient felt almost as though she spoke two languages.

Her shyness was aggravated by the seclusion of her childhood, her sense of inferiority, and her fear of strangers. At the age of 18, even though she had few friends and lacked even a measure of social poise, her mother insisted that she be formally presented to society. The evening of her debut was one of the most memorable and painful of her life. She was not asked to dance and, significantly, was left alone, her head bowed in humiliation.

Defense Mechanisms.—In addition to the apprehensive concern that she might do or say something that her parents would criticize, the patient came to fear that each gesture or word had magical significance as an implement of aggression which could explosively alter any relationship. She acquired an ambivalence to match the shifting feelings of her mother but reacted with intense guilt to any negative affect she experienced. Thus, out of fear and guilt, it became necessary to mask her feelings. No one must know how she really felt about things. Anger and sadness had to be denied, and, as the years progressed, she acquired a superficial social attitude, a bland, pleasant neutrality, which she called her "velvet armor," which no one could penetrate. At moments of crisis, she responded with detachment rather than with appropriate emotion.

This defense of emotional and social isolation continued into her marriage, where communication with her husband was restricted to superficial matters. Feelings of ambivalence were no longer perceived as she grew older; instead, she was troubled with transient depressive periods. She would frequently awaken in the morning with an uncanny sense of guilt, as though she had done something wrong. When the eldest son was born, she looked upon him as a kind of personal fulfilment and thought that through his future achievements she would find a vindication of her unknown guilt. However, as the boy grew to manhood, she recognized some of the paradoxical characteristics of her dead father—intelligence, charm and personal warmth, coupled with eccentricity, irresponsibility, indifference, and homosexuality. With intense conflict, she repressed her fear and ambivalence toward the son whose failure to fulfil her early hopes had disappointed and angered her.

Treatment.—The primary objective in psychotherapy was to clarify the meaning and function of her tics. This was achieved in three ways: (1) by investigating the chronology of the symptoms in order that the onset of the tics might be correlated with life situations or crises; (2) through understanding the symbolic significance of the tic movements themselves, and, finally, (3) by determining the affect, thought, or emotion which had been isolated.

At first the patient was completely unable to associate events in her life with the peculiar disabling contractions of her lips and flexions of her head. However, during the several months she was seen in daily interviews, this objective was at least partially attained. She came to understand the significance of her symptoms and became an active participant in the treatment. "There is a difference between what we do remember, what we think we remember, and what we want to remember," she finally summarized.

The significant historical correlations of her tics were reconstructed as follows: In the fall of 1944, while the patient was living in a respectable community and was maintaining her precarious, superficial adjustment, her niece one day appeared at her house to live with her. The girl had been in both mental and penal institutions, and the patient's initial response was one of

shame, followed by guilt because of fancied disloyalty to her sister's daughter. Shortly after moving in, the girl caused the patient intense embarrassment through antisocial exploits. Several weeks later the malignant mass was discovered in the patient's right breast. The loss of the breast was exceedingly traumatic. While pregnant, many of her feelings of doubt and self-rebuke had been alleviated, and she felt as though she were fulfilling an obligation and expiating some sort of guilt over her shortcomings. Particularly when she nursed her children did she experience a feeling of satisfaction and of vindication. She herself had continued to use sucking as a principal source of gratification. The breast also represented her sexual attraction for her husband, and the sole link which she felt held them together. Within a single month she had been shamed by her niece and had been threatened with the loss of her breast. At this time the twitching, sucking movements of her lips developed.

About a year later, the patient experienced severe depressive reactions. Each morning she awakened with an overwhelming, unattached feeling of guilt. "Have I said something wrong?" she asked herself. The niece had been sent away six months previously, but the patient's alcoholic sister had replaced her. The sister was epileptic and periodically psychotic. Again, because of guilt, the patient nursed (sic) the sister until her death, which occurred shortly before the head tic appeared.

The depression deepened after the sister's death. She felt useless, and the feelings of self-contempt returned. Now there was no one left to nurse. After a confinement in which she had "lost her milk" she had experienced similar feelings of worthlessness. Then came the final deprivation, an artificial menopause.

Six months later, an aching in the muscles of the neck appeared, which coincided with her first knowledge that the eldest son had been expelled from college. She again felt humiliated, worthless, ashamed. Afraid to face anyone, unable to admit her anger toward her son, the flexion spasms of the head began.

The patient was able to recognize that avoidance, withdrawal, and isolation were not only painful neurotic symptoms, but also distinct ways of handling threatening situations. This introduced the patient to the notion that her symptoms were actually measures of defense, and that the tic movements could similarly be understood. The second phase of the treatment, although all three phases proceeded concurrently, consisted of the symbolic interpretation of the tics.

It was clear that the lips had a special libidinal significance in the act of sucking, and in suckling or nursing others. Closely related, then, was the loss of the breast, which represented an actual threat to her life, a profound trauma, and an instinctual deprivation. The repetitive mouth tic was interpreted as an automatic reenactment of the pleasures of sucking and a tenacious preservation of one of the most important sources of emotional gratification. Defensively, the tic was an effort to master the trauma associated with losses she had sustained by repetitively reproducing the acts that had been associated with pleasure and had given her a feeling of purpose and value.

When this was clarified, together with her difficulty in communicating with others, she related that her husband's deafness made it necessary for him to read lips. The tic of the lips had made conversation even more limited. Hence, the movements had been a further defense against letting him know how she really felt. The "tongue like a viper" phantasy had evidently determined this symptom at an early age.

The flexion spasms of her head were treated similarly and interpreted as methods of defense. She reported the various situations in which the position of her head had reflected certain emotional attitudes, such as hanging her head in shame, casting her eyes downward whenever she encountered strangers, whom she invariably feared, or bowing her head when she was reproached by her mother. In general, the head flexion created the illusion of being alone and isolated, safe from strangers, rebukes, and painful situations. It was also an outward response to unacceptable emotions within herself; it was an expression of guilt. One day she had several facial moles removed. She experienced a sudden relief of depression and guilt. Again, this signified the possibility of "facing" people without shame. The tic of head flexion, or, rather, the compulsive urge to hide her face, it will be recalled, developed when her son, who was to have vindicated all her guilt and inferiority, failed in school. She simultaneously blamed herself and reproached herself for suddenly becoming aware of intense hostility toward the son.

After the defensive function of the tics was demonstrated to her, the third phase of the therapy was directed to the emotions and attitudes they protected her against. The objective was also to recover the affects which had been isolated from the ego and to attach them to their appropriate psychic contents. Naturally, many of her reaction formations had to be understood in terms of the emotion which they were designed to conceal. She gradually disclosed her intense ambivalence toward the people she wanted most to love: her parents, sister, and son. Finally, through her relationship to the therapist, who himself stuttered, the patient realized that she need not "face" problems alone, that she need not "hang her head in shame," that she was not likely to "destroy someone with her tongue," that ambivalence was a feature of all intense relationships, and that she could relate to people on a basis other than suckling or nursing them. She discovered that her husband was delighted to share her problems, and she was surprised when he did not reproach her for expressing ideas contrary to his. Two languages were no longer necessary. Similarly, she was encouraged to adopt a more realistic attitude toward her son, after she understood her neurotic expectations of him. All this contributed to an increasing awareness of her own worth. Subsequently, her social relationships altered to the extent that she participated actively in groups of strangers, as hostess and friend, with decreasing fear and shame.

The tics were directly interpreted to the patient by the therapist on the basis of the situations in which they had developed and in terms of the emotional attitude they defended her against. Alleviation of the symptoms was striking. When occurrences came, the concomitant situation was clarified, and the defensive function of the tic was again directly interpreted to her. When the rejected attitude or emotion was disclosed, recrudescences of the tic defenses became more and more infrequent.

The second case illustrates the close affinity of obsessional ideas, compulsive acts, and tics. The fragmentary history of the tic was reconstructed from the interview material provided by a 35-year-old man during a two-year period of psychotherapy for an obsessive-compulsive neurosis.

CASE 2.—*Respiratory tic ("laryngospasm") in childhood, which developed into a swallowing compulsion in later life, associated with periodic recurrence of the original symptom.*

When the patient was 5 years old, he had laryngeal diphtheria. At the time, his father was living apart from the family, and his sister had not yet been born. During his illness, his mother was constantly at his side, and he enjoyed the exclusive attention that his illness required. When the diphtheria was finally overcome, a respiratory tic remained. This consisted of a perpetuation of the original dyspnea, arching of the neck, and twisting of the mouth in anguish, while uttering a gasping, stertorous cry. In retrospect, he recognized that the tic, which he was powerless to control at the time, was an effort to feign respiratory distress and thus insure his mother's exclusive devotion. Nevertheless, the pleasure he derived from his mother's care was incomplete. When she took him for a ride, the little boy was bundled up so securely that again he became afraid of suffocation, as he had been when actually suffering from diphtheria.

As the patient grew older, the fear of suffocation and strangulation remained. Occasionally his nights were disturbed by compulsive thoughts that he had "swallowed something the wrong way" and would suffocate in his sleep. Often he awakened in the night with "croup" or "laryngospasm," simultaneously gasping and crying like a lonely, fearful, and deserted child until his wife came in to comfort him. Such attacks occurred whenever he was threatened with separation from someone close to him.

The fear of choking had early become associated with fear of separation from his mother. As his obsessional neurosis became elaborated in later years, he began to blame himself for any misfortune, however impersonal, that occurred. By devious rationalization, he was able to trace certain unhappy events, such as death, illness, or injury, to his own shortcomings and misdeeds. Thus, by magical means, he felt obliged to forestall evil events. Whenever he thought of death, or saw a picture of a dead person, or read about disasters, he felt compelled to swallow a fixed number of times, corresponding to the number of living persons in his family. As his neurosis became severer, the mere presence of "bad thoughts," i. e., sexual or aggressive phantasies,

induced compulsive swallowing to prevent the loss of someone dear to him through death or separation. The nocturnal "laryngospasm" was often precipitated by his fear of being alone and deserted, as a kind of atavistic return to the cry of the postdiphtheritic days, when he was afraid of losing his mother. The compulsive swallowing was also designed to forestall desertion, this time because he had been "bad."

Closer examination of the patient's punitive conscience (universal guilt, implicitly containing phantasies of omnipotence) and dreaded instinctual impulses finally disclosed that basically the patient was struggling against the wish for his father's death. This was the repressed counterpart of his wish to have mother exclusively for himself and of his fear of desertion. His guilt over these wishes supplied a motivation for the fear of strangulation.

The respiratory tic of childhood and the "laryngospasm" of adult life were functionally related. The fear of strangulation not only was the result of diphtheritic dyspnea but also was a reprisal for hostile impulses against his father. Although the patient feared separation from his beloved mother, the tic restored a gratifying situation. Even as an adult, it represented a partial repetition of the conflictual event. The death wishes were neutralized by elaborate

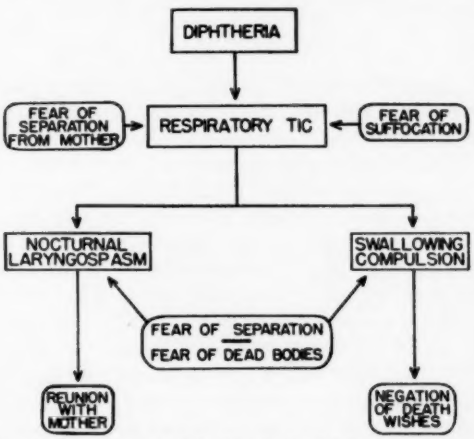

Fig. 1.—Transformation of a postdiphtheritic tic in childhood into nocturnal laryngospasm and compulsive swallowing.

precautionary measures, including the compulsive swallowing. The conflict was thereby "split," with respect to neurotic defenses, into the wish for mother, represented by the tic, and the destructive urges against the father, which he attempted to control through the swallowing compulsion (Fig. 1).

CASE 3.—*Multiple tics of the head, neck, and extremities.*

A 27-year-old salesman complained of tics involving all parts of the body. The movements had been present since early adolescence. They consisted mainly of abrupt, ferocious grimaces of his face in which the corners of his mouth were suddenly drawn down, exposing his teeth. In addition, his head would tremble violently, as if all the muscles of his neck had simultaneously gone into contraction. Accompanying these major movements, a wave of muscle spasm quickly passed through the rest of his body, giving an appearance of both writhing and shuddering. The left shoulder, arm, and hand periodically flexed spasmodically. This series of movements constantly repeated itself and resembled the preparation a person makes prior to striking a blow. The tic being thus interpreted, his fist clenched, his shoulders contracted, and his face was distorted with rage, while the entire body shuddered with movements of anticipatory anger and fear.

The family history disclosed that he was the youngest child and only son of parents who were middle-aged when he was born. There was an older sister, who had also suffered from tics in

adolescence. His relationship with her was characterized by hostility in adolescence and exaggerated solicitude in adulthood. He had grown up in a "dead-end" slum, surrounded by poverty and crime. One of his earliest memories was that of seeing the body of a dead prostitute who had been murdered by a sailor. He reacted to this sordid environment by withdrawal and seclusion, devoting himself to ambitious plans for the future. In later years, he realized that his parents could have afforded to live in another section of the city, but he experienced no conscious resentment over their neglect.

Overt expressions of resentment or aggression were under strong repression. On a single occasion, when he had been provoked into a fight, he beat his opponent so savagely that the man went to the hospital with multiple fractures. When this was discussed in interviews, he associated loss of temper with insanity and loss of all control.

The interpretation of the tic pattern as a momentary display of aggression determined the goal of therapy. Consequently, the patient recognized some of the latent hostility within himself and the objects against which his hypothesized anger was directed. Subjectively, his tics seemed at first entirely adventitious and were accompanied by no affect other than "nervous tension." He had many of the characteristics of the obsessional neurosis, but few, if any, rituals. The chief mechanisms of defense were isolation, undoing, and reaction formation.

COMMENT

Differentiation from Neurological Diseases.—Tics must be differentiated from the abnormal muscular movements occurring in various neurological diseases. Patients with early Huntington's (chronic) chorea may display repetitive facial grimaces and twisting movements of the head and neck, which may be associated with emotional and intellectual abnormalities. In the absence of a family history, the differential diagnosis may be difficult. However, the lack of concomitant obsessional character traits and compulsive acts suggests that the motor disturbance of Huntington's chorea is determined by nonpsychological factors, although, certainly, all extrapyramidal disorders can be temporarily modified by various emotions. The patient with Huntington's chorea can further be distinguished by his almost complete inability to control his symptoms and by the lack of anxiety or feelings of mounting tension in those cases in which some restraint is possible.

The individual movements of Sydenham's (minor) chorea, when viewed apart from the whole, may resemble tics. However, tics are characteristically repetitive and tend to be confined to a single functional unit of movement. Sydenham's chorea involves many muscular movements, which seldom are duplicated. In addition, chorea is usually associated with a gross exaggeration of all normal gestures and general disturbance of motility. Objective signs of disturbance of muscle tone, coordination, and reflex activity are often noted in chorea but are absent in psychogenic tic.

The periodic twitches of clonic facial spasm may show some gross similarity to facial tics. The muscle contractions, however, are those characteristic of abnormal innervation, with fleeting spasms which voluntary acts cannot reproduce. The movements are almost continuous and cannot be controlled by will. What surcease the patient finds is not associated with any anxiety, and the patients derive no satisfaction from performing the movements. These differential points apply equally well to myoclonic jerks, which in specific instances may be confused with tics.

Tics must be separated from stereotyped acts and personal mannerisms. Many healthy persons display various aberrant movements in the course of certain activities. A man who licks his lips when concentrating, who wrinkles his nose when listening intently, or who absentmindedly scratches his head is not necessarily

suffering with tic. Throat clearing, sniffing, "nervous" coughing, crossing and uncrossing one's legs, restless shifting about, belt hitching, shoulder shrugging, and other such motor acts may be merely indications of temporary restraint. These may occur in various situations, such as when one is obliged to listen to a dull paper, is confined in an unpleasant atmosphere, or even concentrating on a problem. Such mannerisms or stereotyped acts differ from tics in that they can be inhibited indefinitely and neither anxiety nor conflict results from such restraint. There is no compulsive urge to carry out the movements, and hence no satisfaction in their performance.

Relation of Tics to Obsessional Neurosis and Hysteria.—The frequent occurrence of obsessional symptoms and compulsive rituals in patients with tic suggests a common pathogenic basis. In some instances, such as the second case, the actual transformation of a tic into a compulsive act may be observed. It is likely that the tic and the obsessional neurosis are allied efforts to cope with the same repressed affect.

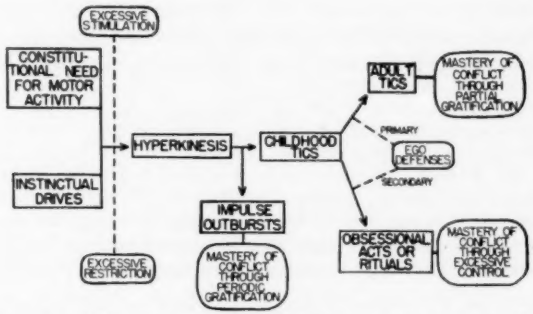

Fig. 2.—Factors in childhood tics and their relation to adult tics, impulse outbursts, and obsessional acts and rituals.

In many instances tic consists of a partially repressed erotic or aggressive drive and a motor defense against it. Gratification of the impulse occurs in a fragmentary way through the partial reenactment of the episode in which the drive was originally expressed. The tic may be the repetitive reenactment of a traumatic event, the satisfaction of an instinctual drive, or the reproduction of a conflictual situation. The incomplete act serves as a token discharge, or symbolic representation, of an unresolved conflict, situation, or impulse. Under the influence of the defense mechanism of isolation, whatever emotion persists in the act is removed, thus enabling the tic to continue into adulthood as an autonomous phenomenon. In one patient, a forbidden interest in excrement in childhood persisted as a curious nose-wrinkling and snorting tic, which investigation showed was the defensive rejection of the odor of feces.

As the person matures, other defensive measures become available and alter the methods by which instinctual drives may be satisfied. The conflictual situation may be translated into purely psychic phenomena, such as obsessional thoughts, doubts, pathological cleanliness, or preoccupation with trivia. Reaction formation, sublimation, modification or reversal of aim, and displacement of object are general mechanisms which facilitate the change. Other types of defense, such as denial by

word or act, undoing, or intellectualization, may also occur. All these mechanisms, and undoubtedly others, contribute to the development of the compulsive ritual, which is a series of acts designed to protect the individual from the guilt or anxiety of a repressed impulse.

Both the tic and the compulsive ritual are ideomotor acts; both serve as defensive gestures against a warded-off trauma or conflict. The tic characteristically develops in the immature individual before the intellectual ability and integrative capacity for mastering anxiety have fully developed. With limited defenses, the traumatic event is repeated in a fragmentary way. In contrast, the compulsive ritual is designed not to permit discharge of strong emotional drives, but to master them completely (Fig. 2). The hand-washing compulsion is frequently determined by the wish to rid oneself completely of the "dirt" entailed in phantasies of sexual or aggressive activities. The compulsive ritual deals frequently with symbolic conflicts rather than with traumatic or excessively stimulating experiences. It usually involves personal relationships, while the tic is often related only to the integrity of the individual. It has been stated that "symbolic tics" are really pseudo tics, inasmuch as the more objectionable component impulses are not expressed.[15b] There are many instances, however, in which this distinction is maintained with difficulty, as in Case 4.

Case 4.—A 30-year-old man exhibited a tic of the head, in which he abruptly jerked his head back and looked upward. He would then look downward with his eyes partially closed. Study disclosed that the tic had developed when, as a young boy, he saw his aunt descending the stairs. He had looked upward suddenly and was both alarmed and excited when he saw her genitals. The secondary component of the tic, the looking downward with eyes lowered, was clearly an effort to deny what he had seen. The upward jerk of the head with eyes looking upward was an attempt to resurrect the experience and to reproduce the scoptophilic excitement.

In this case is the act a tic or a compulsive ritual? In my opinion, the tic and the compulsive ritual cannot be considered apart from the ego of the afflicted person. The capacity of the ego to develop and use a variety of defense mechanisms and to permit instinctual drives to be expressed, with neither anxiety to the person nor harm to the external world, is a measure of maturity. The system of defenses which is employed probably determines, to a large extent, whether a conflict is expressed as a tic, a compulsive ritual, or an obsessional thought. The relationship of the various motor symptoms may be thought of as a spectrum. The tic, at one extreme, is a partial representation of the original impulse, which has been inhibited in its full expression. At the other extreme is the compulsive ritual, which is a protective act to avert the anxiety or guilt entailed in the recognition of the repressed impulse. Between the extremes, various proportions between impulse and defense exist. In this sense, tics are rudimentary rituals; rituals are elaborated tics.

Some authors [17] believe that the tic is a pregenital conversion symptom, in that the affect is bound to an erogenous zone with anal-sadistic importance. In addition, the defensive function of the tic should be stressed because it enables the repression to be maintained and the conflict resolved, through undoing, denial, displacement, isolation, or fragmentary symptomatic acts in order that the unacceptable impulse may be mastered.

17. Abraham.[10] Ferenczi.[11] Fenichel.[16]

As with the compulsive ritual, there are cases of tic which may be differentiated from cases of conversion hysteria only with difficulty. Tics usually represent a more narcissistically oriented aggressive or erotic conflict, which finds partial expression in the symptom after isolation of the affect. Many conversion symptoms consist of erotic phantasies which have been repressed completely. Patients with tic have more conscious control over the symptom than do patients with hysterical motor phenomena, but this is not an invariable distinction. Indeed, where functionally related muscle groups are involved, differentiation may not be possible, even on theoretical grounds.

Treatment.—The detailed therapy of the patient with tic has been presented in Case 1. This procedure was followed with all the patients reported. The focus of the treatment was directed toward understanding and interpreting the tic as a defensive act.

Whenever possible, the chronological relation of the development of the tic to various life situations and emotions should be clarified. However, in many cases, the appropriate affect has been isolated, and only the motor symptom remains. In this way, the tic is analogous to the isolated obsessive thought or compulsive ritual, which is often manifested in an affectless atmosphere with considerable intellectuality, doubt, or disbelief. The first task of therapy, then, in such cases is to clarify the defensive function of the symptom itself. The task of reuniting the appropriate affect with the defensive symptom is usually prolonged, and even then is not often associated with therapeutic success. Therefore in treating patients with tic I have followed the procedure of understanding the symbolic significance of the tic pattern as early as possible in the course of treatment and interpreting it directly to the patient. This may facilitate the patients' recognition that the apparently meaningless movements serve to protect them against some unpleasant emotion. In this way, the woman in Case 1 was told quite directly, "You hang your head as if you didn't want to be seen," and later, "If you hide your face, no one can see how you feel." In Case 3, the patient was informed that his facial grimaces and clenched fist looked as though he wanted to punch someone. The man who had the tic in which he abruptly looked up and then down was asked, "What are you afraid to look at?"

Sometimes the direct inquiry or interpretation was a tour de force into preconscious recollections. In most instances, however, these provocative inquiries led to other material, which enabled the therapist to determine, with greater accuracy than his intuition afforded, the nature of the isolated affect or the defense method. Gradually, historical data can be accumulated, and this, too, will often disclose relationships not previously seen. Another source of information comes through witnessing the actual occurrence of the tics in association with the discussion of certain topics.

CASE 5.—A 42-year-old man suffered with paroxymal throat clearing. It was noted early in the treatment that the tic occurred whenever he spoke of a topic associated with resentment. Later, this focused about matters relating to his mother. The tic finally disappeared when his intense hostility toward his mother became clarified. Moreover, he became aware of a wish to throttle her and hear her struggle for breath. This wish was graphically represented in the tic by the manner in which he cleared his throat.

In this instance the defensive function of the tic was not understood until the isolated or repressed hostile affect was demonstrated. Whether the defense or the impulse is considered first, later they are always spoken of together.

Sometimes the relation between tic and an intolerable conflict becomes evident to the patient, without interpretation, early in treatment, as in Case 6.

CASE 6.—A 52-year-old man was referred to the psychiatrist with the complaint of irresistible "teeth clicking." Although the symptom was apparently trivial, it prevented the patient from wearing dentures and thus was indirectly associated with considerable social and dietary difficulties. Investigation disclosed that the symptom had begun years before, as he watched the body of his closest friend being lowered into the grave. He gritted his teeth in order to fight off tears, inasmuch as he prided himself on the stoic manner in which he handled all calamities. The dead man had been his most intimate friend. Together they had shared poverty, and together they had built up a thriving nation-wide business. But just when their success had finally seemed assured, the friend had died of a painful, debilitating disease. "Just when things finally began to 'click,' he died!" The tic was a literal expression of the patient's thought.

The relation between the tic and the death of his friend was made clear during the second psychiatric interview. After this interview the patient developed considerable anxiety, canceled further appointments, and left town for several days. It was hypothesized that the tic signified more than grief over the loss of his friend. The anxiety evidently was the response to what he considered the imminent disclosure of ambivalent, or even hostile, feelings toward the man, or perhaps even his secret gratification that now the business was completely his own!

Various techniques enabling the affectless subjects to recognize and accept emotional responses in themselves are required. This can often be facilitated by the method of generalization, such as, "Many people would have felt afraid in such a situation. How did you feel?" To indicate the therapist's permissive attitude, anticipatory suggestions may be offered, such as, "It's hard to believe that you weren't angry when that happened to you; it would have been a natural feeling to have," or "You might have been bothered more than you realized at the time." Some modifications in psychotherapeutic approach employed by Eisenstein [18] in treating borderline states are also used when indicated.

One of the constant needs of the patient with tic is always to feel accepted, since the feeling of self-rebuke and inferiority is almost an invariable consequence of perceiving an unworthy emotion. The need for ego support is strong, and when the anxiety mounts or the depression that accompanies certain phases of the treatment becomes marked, it is permissible to encourage the patient in order to augment his more intellectual defenses. In a sense, then, the psychotherapy of the patient with tic often consists in transforming the symptom into a psychic, rather than a motor, defense, and thereby changing the disorder into a more tolerable form of obsessional neurosis.

SUMMARY

By definition, the tic consists of abrupt, rapid, repetitive movements of functionally related groups of muscles. It is associated with an intolerable mounting tension unless the urge to perform the movements is obeyed, after which a temporary gratification is experienced. The tic is subject to voluntary control for varying periods of time, but always with an accumulation of inner tension. In this descriptive sense the tic is similar to the compulsive act or ritual, since both phenomena display increased anxiety or tension followed by gratification. This is not characteristic of the motor symptoms of conversion hysteria and may be an important clinical distinction.

18. Eisenstein, V.: Differential Psychotherapy of Borderline States, Psychiat. Quart. **25**:379, 1951.

If the impetus for the tic is a recurring instinctual drive, or a memory trace of a traumatic or conflictual situation which has the need of abreaction, then the alternation of tension and gratification becomes comprehensible.

Tics occur more frequently in children than in adults. The inadequacy of the maturing ego to cope with excessive stimulation from within, or undue restraint from without, actually refers to the limited number of defense mechanisms available to the child. In the most primitive sense, the earliest (primary) defense mechanisms operate on the sensory and motor level, and the resultant is expressed in terms of action (ideomotor).

The adult ego has manifold differentiated (secondary) defense mechanisms (Fig. 2), and, as a result, conflict and solution are represented in symbolic, purely ideational, terms. The tic is the resultant of preliminary defensive efforts of the ego to cope with specific tensions. It is a partial act, a fragment of primitive motor responses, which recurrently thrust themselves forward. Only by partial inhibition, restriction, or isolation of the affective content does the ego maintain control. Instead of a furious, homicidal assault (Case 3), a snarling grimace and a clenched fist remain as affectless relics. In Case 1 a mouth tic provided the restitution of a gratification of sucking and suckling in the face of a conflict.

The treatment of adult tics, as described in this paper, emphasizes the direct interpretation of the defensive function of the tic, in an effort to disclose the isolated affect and permit elaboration of the patient's psychodynamics. The adult tic, thus closely allied to the compulsive act or ritual, is viewed as a fragmentary reenactment of a conflict situation, seeking periodic expression.

FRONTAL LOBOTOMY IN A SCHIZOPHRENIC PATIENT WITH ADVANCED HYDROCEPHALUS

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IT IS THE purpose of this report to describe a case of severe schizophrenia in which certain psychotic manifestations were greatly reduced by prefrontal lobotomy, despite the presence of advanced hydrocephalus. A search of the literature reveals no instance in which a patient with such extreme hydrocephalus has been subjected to lobotomy, and for this reason the case is believed to be unique.

The Boston Psychopathic Hospital Group,[1] on the basis of their review of the literature, concluded that, except for mental derangements appearing with epilepsy, psychoses associated with organic cerebral changes have generally not profited from lobotomy. These investigators described three of their own cases in which obsessive-compulsive features were relieved by the operation, although each patient had evidence of organic damage, as indicated by preoperative psychometric studies and by gross "cortical atrophy" noted at operation. Pneumoencephalographic studies were not performed. Their series also included 13 cases with signs or symptoms suggestive of brain damage secondary to meningitis, encephalitis, head injury, idiopathic cerebral atrophy, or convulsive seizures, and a "good mental status" resulted in only one of these cases.

The experience of Freeman and Watts [2] led them to believe that organic brain disease is not a contraindication to lobotomy, although the results are not likely to be as good as in an uncomplicated psychosis because the increase in unrestrained behavior leads to difficulties in social adjustment. Included in their series were cases of Parkinsonism, Huntington's chorea, postencephalitic behavior disorder, epilepsy, cerebral thrombosis, birth palsy, familial spastic paraplegia, head injury, and multiple sclerosis.

The series of Partridge [3] included six cases with organic features in which lobotomy was performed. Considerable improvement was obtained in a case of

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1. Greenblatt, M.; Arnot, R., and Solomon, H., Editors: Studies in Lobotomy, New York, Grune & Stratton, Inc., 1950.

2. Freeman, W., and Watts, J. W.: Psychosurgery, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1950.

3. Partridge, M.: Pre-Frontal Leucotomy, Springfield, Ill., Charles C Thomas, Publisher, 1950.

postencephalitis with obsessional symptoms and in a case of schizophrenia with an old head injury, and less pronounced benefit in a case of severe behavior disorder associated with cerebral palsy. There was temporary improvement in the obsessive-compulsive symptoms in a case of "presenile dementia," but this was followed by a rapid increase in the dementia. In a case of manic-depressive psychosis with insidious senile changes there were a reduction in the intensity of the behavior disturbance and only a very gradual increase in the senile mental deterioration. There was ultimate improvement in a case of undifferentiated psychosis with an organic flavor without an increase in organic features.

Upon the basis of their experience with individual cases of psychoses with post-encephalitic Parkinsonism, dementia paralytica, muscular dystrophy, and congenital cerebral palsy, Worthing and associates [4] concluded that the therapeutic response to lobotomy was not notably different from that seen in "functional cases" with similar symptoms. No intensification of the primary organic condition or increased tendency toward "disinhibition" was noted.

Unfavorable results led Frank [5] to consider organic cerebral deterioration from arteriosclerosis, senility, or dementia paralytica as a contraindication to lobotomy. Solomon [6] found that arteriosclerotic patients were poor subjects for lobotomy, but that advanced age in itself did not prohibit good results. Myerson and Myerson [7] also obtained good results in patients over 60, and Gayle and Fishburn [8] reported "unexpectedly good" results in patients with psychoses diagnosed as senile and arteriosclerotic.

That epileptic psychoses were benefited without the frequency of the convulsions being influenced was reported by Hofstatter and associates,[9] Yahn,[10] Ström-Olsen and associates,[11] Freeman and Watts,[2] Tancredi and Mattos Pimenta,[12] and Fiamberti and Cameroni.[13]

4. Worthing, H. J.; Brill, H., and Wigderson, H.: Evaluation of Immediate and Late Results of Prefrontal Lobotomy in 600 Cases, Including a Case of Post-Encephalitis and Other Organic States, Am. J. Psychiat. **108**:328, 1951.

5. Frank, J.: Clinical Survey and Results of 200 Cases of Prefrontal Leucotomy, J. Ment. Sc. **92**:497, 1946.

6. Proceedings of the First Research Conference on Psychosurgery, New York, Nov. 17 and 18, 1949, Washington, Public Health Service Publication No. 16, 1951.

7. Myerson, A., and Myerson, P.: Prefrontal Lobotomy in the Chronic Depressive States of Old Age, New England J. Med. **237**:511, 1947.

8. Gayle, R., Jr., and Fishburn, G.: Prefrontal Lobotomy, Dis. Nerv. System **9**:242, 1948.

9. Hofstatter, L.; Smolik, E. A., and Busch, A. K.: Prefrontal Lobotomy in Treatment of Chronic Psychosis, with Special Reference to Section of Orbital Areas Only, Arch. Neurol. & Psychiat. **53**:125, 1945.

10. Yahn, M.: Leucotomy in Epileptic Syndromes, Neurobiologia **9**:170, 1946.

11. Ström-Olsen, R.; Last, S. L.; Brody, M. B., and Knight, G. C.: Results of Prefrontal Leucotomy in 30 Cases of Mental Disorder, with Observations on Surgical Technique, J. Ment. Sc. **89**:165, 1943.

12. Tancredi, F., and Mattos Pimenta, A.: Leucotomia pré-frontal em esquizofrénicos, epilépticos e psicopatas: Observações sôbre 76 casos operados, Arq. neuro-psiquiat. **7**:141, 1949.

13. Fiamberti, A. M., and Cameroni, V.: Epilessia e leucotomia prefrontale transorbitaria, Sis. nerv., Vol. 2, March-April, 1950.

Schwartz [14] achieved marked improvement in a chronically depressed patient with postencephalitic Parkinsonism. Rizzatti and Borgarello [15] and Thorpe [16] reported postencephalitic behavior disorders to be favorably influenced. Engler [17] found only 3 of 43 mentally defective patients with conduct disorders significantly improved after lobotomy. Mackay [18] reported upon a similar group of "psychopathic feeble-minded patients," among whom were 2 with epilepsy, 5 with postencephalitis, and 13 without a demonstrable organic condition. Four of the seven patients with "organic" disease were considered "improved," whereas seven of the patients with an "uncomplicated" condition were "markedly improved" and three were "improved" after the operation.

Donovan and associates [19] performed lobotomies on 12 schizophrenic patients whose preoperative encephalograms revealed abnormalities in the form of various degrees of ventricular enlargement or widening of the sulci or cisterns, or a combination of these changes. Significant improvement was obtained in only one of these patients.

An "abnormal cortex" was an incidental operative finding in "less than 10%" of over 500 lobotomies performed by Poppen [1] and in 10 of 531 lobotomies by Freeman and Watts,[2] but no statement was made as to the correlation of the clinical results with these changes.

Yakovlev [1] reported atrophy in four of six brains of lobotomized patients who died from 11 to 235 days after operation. He found correlation between the severity and duration of the social invalidism and the degree of cerebral atrophy and concluded that a more or less severe atrophic process was present before operation. Some doubt is cast upon this interpretation by the study of Meschan and Scruggs,[20] who performed pneumoencephalographic studies shortly before and up to 20 months after lobotomy in 19 patients and correlated the changes shown with autopsy findings in 7 other patients. Regardless of preoperative findings, the lobotomized patients showed pneumoencephalographic evidence of progressive dilatation of all the ventricles and obliteration of the subarachnoid spaces. In five of seven cases studied at autopsy there were noted atrophy and gliosis throughout the brain and generalized enlargement of the ventricles, most prominent in the frontal horn.

REPORT OF A CASE

B. O., a divorced woman aged 28, was admitted to the Langley Porter Clinic on Feb. 14, 1950, as a transfer from a nearby state hospital for consideration of a prefrontal lobotomy for a chronic schizophrenic illness. The patient was too disturbed to give details of her past history;

14. Schwartz, E.: Depression in Parkinsonism Treated by Prefrontal Leucotomy, J. Ment. Sc. **91**:503, 1945.

15. Rizzatti, E., and Borgarello, C.: Duecento malati di mente operati di leucotomia prefrontale alla Moniz, data statistici e clinici, Nevrasse, Torino **1**:11, 1940.

16. Thorpe, F.: Prefrontal Leucotomy in Treatment of Post-Encephalitic Conduct Disorder, Brit. M. J. **1**:312, 1946.

17. Engler, M.: Prefrontal Leucotomy in Mental Defectives, J. Ment. Sc. **94**:844, 1948.

18. Mackay, G. W.: Leucotomy in the Treatment of Psychopathic Feeble-Minded Patients in a State Mental Deficiency Institution, J. Ment. Sc. **94**:834, 1948.

19. Donovan, J. F.; Galbraith, A. J., and Jackson, H.: Some Observations on Leucotomy and Investigations by Pneumoencephalography, J. Ment. Sc. **95**:655, 1949.

20. Meschan, I., and Scruggs, J. B.: Pneumoencephalographic Changes Following Prefrontal Leukotomy (Freeman-Watts Technic), A. M. A. Arch. Neurol. & Psychiat. **65**:60, 1951.

but, according to the mother, there was no family history of mental or nervous disorders; her birth and early development were normal, and there was no history of any major illness. Upon specific questioning, it was found that her mother was unaware of any abnormality in size or contour of the patient's head. She could recall no early difficulties, such as would be expected in a congenitally hydrocephalic child, and no childhood illness which could have resulted in acquired hydrocephalus. The patient was an only child and was always unduly close to her mother, being childishly jealous of any interest shown by the latter toward any other person. She was reported to have done well in school, having completed high school and one year of college without difficulty by the time of her marriage, at the age of 19. She had few close friends, although she was described as outgoing and friendly. Her marriage proved difficult, owing to the patient's conflict over her sexual role and her husband's meticulous nature and demanding ways.

In 1943, at the age of 21, the patient became mentally ill, was hospitalized for eight months, and received electroconvulsive therapy. After her discharge the patient returned to her husband, but their difficulties continued and led to his obtaining a divorce. The patient became upset, but finally was able to settle down sufficiently to work as a housekeeper and baby sitter. In June, 1947, she became seclusive and preoccupied and expressed hallucinations. After receiving five electroconvulsive treatments on a private basis and six in a county hospital, without improvement, she was readmitted to a state hospital on July 29, 1947, with a diagnosis of schizophrenia, paranoid type. She remained hospitalized, and by the time of her transfer to the Langley Porter Clinic she had received 46 additional electroconvulsive treatments, with only slight, transient improvement.

On admission, she was loud and belligerent, constantly expressed ideas of persecution and extreme fear of electroconvulsive treatments, and appeared to be responding to hallucinations. She was suspicious of the staff and of the other patients and repeatedly cornered one staff member after another, asking the same questions and being unable to accept reassurance. She was unable to cooperate for laboratory studies except under heavy sedation. Because of her disturbed behavior, it was necessary to administer five electroconvulsive treatments during the first 12 days after admission.

Physical examination revealed a condition consistent with long-standing, compensated hydrocephalus. The skull was brachycephalic and enlarged. The optic disks appeared somewhat yellow, and there was marginal gliosis. The rest of the physical examination was noncontributory. The patient was unable to cooperate for psychological tests.

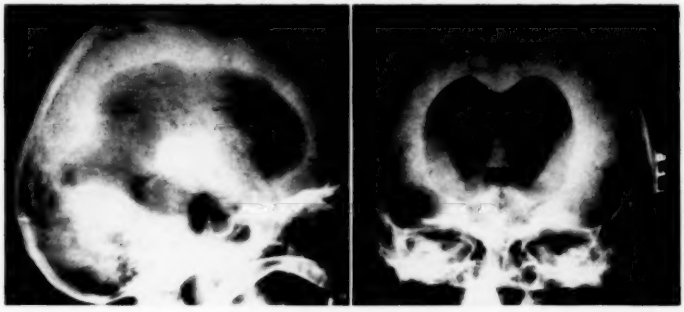
Laboratory studies gave essentially normal results except for findings related to the hydrocephalus. An electroencephalogram, obtained while the patient was under sedation with 0.5 gm. of amobarbital sodium, was unsatisfactory, owing to movement artifacts and the effects of the sedation. A pneumoencephalographic study was made, in the process of which 300 cc. of cerebrospinal fluid was removed. This study showed a very pronounced dilatation of all the ventricles, including the aqueduct and the fourth ventricle, and being somewhat more pronounced on the right side. The pontine cistern was well demonstrated and was enlarged. Little air was present over the convex surfaces of the brain (Figure). After this procedure the patient complained continually of "water sloshing about" in her head. Roentgenograms of the skull taken 10 days later showed residual air in the lateral ventricles. Throughout this period a splashing sound could be elicited by shaking the patient's head.

On March 15, 1950, bilateral prefrontal lobotomy was performed through 2½ in. (3.8 cm.) bone flaps placed at the coronal-suture line and extending to the insertion of the temporal muscle. The arachnoid was found to be considerably thickened, and this finding, together with the results of the pneumoencephalographic studies, indicated that the hydrocephalus was due to a post-infectious adhesive arachnoiditis. The entire gyrus lying anterior to the coronal-suture line on the left was removed for metabolic and microscopic study.[21] After this, the white matter on the left was sectioned in a plane with the sphenoidal ridge until the ventricle was reached. Upon entering the ventricle, it was noted that only a few fine strands of tissue were left as remnants of the septum pellucidum. Both foramina of Monro were dilated to at least 0.5 cm. in diameter.

21. The only definite change noted upon subsequent histological study of this small section was rarefaction of the cortex, the nerve cells being more widely dispersed than usual.

After the ventricle was entered, the plane of section was continued just anterior to the caudate nucleus. A similar section was carried out on the opposite side.

The patient was able to respond to questions coherently and relevantly within seven hours after her operation and to take food by mouth the following day. She became lethargic and apathetic and often fell asleep while eating, but could always be readily aroused. Her temperature remained elevated for approximately 20 days, and at various times she showed pronounced cerea flexibilitas, which had not been present prior to operation. Papilledema and retinal hemorrhages were noted on the fifth postoperative day, at which time the deep muscle reflexes on the left were more active than those on the right and there was relative weakness on the left. She responded automatically and without animation, often stuffing her mouth with food without swallowing it, being completely unaware of her incontinence, and mimicking the last word of anything said to her. By April 7, 23 days after operation, she first became ambulatory, moving stiffly and having to be pushed along. She gradually grew more animated and spontaneous and in a month after her operation was eating well and seemed to have a vague, naïve interest in her surroundings. By the time of her transfer to a state hospital, seven weeks after operation, she still required direction at the toilet and constant supervision in the simplest activities, had to be led about, and was able to make only simple verbal responses, such as "You're telling me," "I'll say so."



Lateral and posteroanterior pneumoencephalograms, showing pronounced ventricular dilatation and absence of air over the convex surfaces of the brain.

Six weeks after her return to the state hospital the patient was sufficiently improved to be placed on leave in the care of her mother. She was returned to the hospital after four months because of persistent incontinence.

Psychometric tests on Aug. 24, 1950, five months after operation, revealed "organic" and schizophrenic characteristics. On the full-scale Wechsler-Bellevue test she earned an intelligence quotient of 63; the verbal scale was 75, and the nonverbal scale, 54. Her Healey score showed a similar mental level. Her Human Figure Drawings were psychotic productions, being dysplastic and distorted and with many bizarre features. At this time the patient was in good contact with her environment and cooperative. She was animated and facetious but tended to perseverate.

After being placed on leave on Dec. 21, the patient was seen again on June 11, 1951, 15 months after operation. Her mother reported that she was incontinent approximately twice a week. She described her as irresponsible, prone to occasional temper outbursts, a bit childish, quite cheerful, confident, and "not a bit apathetic." The patient appeared euphoric and laughed frequently during the interview. She had gained 50 lb. (22.7 kg.) and was completely unable to control her appetite. The mother commented upon this, saying that she had recently awakened from an afternoon nap to find that the patient had opened and consumed half a can of beans they had planned to have for dinner that evening. The patient talked freely about her illness but could recall her confusion, fears, and hallucinations only as "dim memories." The mother planned a trip East which would make it necessary for the patient to reenter the hospital on June 21.

In December, 1951, the patient was reported to be making a fairly good ward adjustment. She was irritable with the other patients at times and was occasionally enuretic at night. Although she was generally pleasant and friendly, it was necessary to restrict her activities somewhat because of her poor social adjustment, particularly in the presence of male patients, with whom she was silly, playful, and flirtatious. Psychometric studies done in November, 1951, 20 months after operation, yielded the following results: Wechsler-Bellevue Form II, full-scale intelligence quotient, 80; verbal intelligence quotient, 85; performance intelligence quotient, 78. Healey Picture Completion II, 8½-year level. Her Human Figure Drawings showed much improvement, especially in terms of social awareness, but grossly psychotic signs were still present. In January, 1952, she began to hallucinate again, being quite distracted by the voices, but in a flippant sort of way, and showing none of her former agitation. Her playful, indolent, and unrestrained behavior has continued.

COMMENT

The decision to operate upon this patient was a difficult one to make. The severity and chronicity of the mental symptoms left no doubt as to the psychiatric indications for a lobotomy. However, the immediate surgical risks would be appreciably increased. The borderline absorptive mechanism could be "decompensated" by the introduction of blood and of breakdown products of cerebral tissue into the cerebrospinal fluid; an already damaged brain could poorly tolerate further damage and edema, and the distortion of the normal cerebral landmarks might lead to surgical accidents. From a more remote standpoint, further cerebral damage superimposed on the existing damage might more easily lead to a state of intellectual and physical defect.

In spite of the fact that the organic process was severe, the past school and social adjustment of the patient indicated that her intellectual capacity was relatively unaffected, and at least within normal limits. This factor, along with the considerations that the organic process was a stationary one and the psychiatric indications were high, led to the decision to operate in spite of the increased surgical risk.

The postoperative torpor was both prolonged and severe, and many associated neurologic signs developed; but these changes were transient. At present there is no indication that further organic damage resulted from the operative procedure, despite the presence of advanced hydrocephalus.

SUMMARY

The effect of a prefrontal lobotomy in a case of chronic schizophrenia with extreme hydrocephalus is described. The postoperative picture was characterized by a prolonged state of extreme apathy with "robot-like behavior." Psychometric studies done five months after operation, at which time the state of inertia had largely disappeared, revealed pronounced "organic" and psychotic features. After another 15 months the same studies showed less organic characteristics and a 17-point gain in the intelligence quotient. The psychotic features of the patient's illness were strikingly reduced, but this improvement was tempered somewhat by a lessening of restraint and persistence of bulimia and incontinence, which made the social adjustment somewhat difficult. It is remarkable that so few "organic" signs resulted from the superimposition of a frontal lobotomy upon an already severely damaged cerebrum.

THOUGHT AS A FORM OF SENSATION, AND AGNOSIS OF THOUGHT

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STUDIES on patients with lobectomies, lobotomies, and epilepsy have furnished new evidence that thought is the product of activation of a gigantic, but specific, group of neurones. As Cobb [1] has said recently: "There is no hint of any fundamental difference between the 'mental' and 'non-mental' functions of the central nervous system." Newly reported electrical stimulation of scarred temporal cortex by Penfield [2] has pinpointed the evidence.

Briefly, there exists a "neurointellectual" system which is comparable to the neuromotor and neurosensory systems. The essential difference in the systems lies only in their end-organs, and not in the basic behavior of the central nervous system. Except for the end-organs, and hence the mode of activation and of expression of the neural activity, the neurointellectual system behaves identically with the neuromotor and the neurosensory.

The neuromotor system has the muscles as end-organs. A muscle contraction is concrete, observable, and measurable, and the neural mechanisms underlying it are, therefore, the best known and understood. The neurosensory system has end-organs, the behavior of which is less easily observable; its operations are, therefore, less well known to us. For similar reasons, the neurointellectual system is even less well understood.

The following suggestion for a neurological definition of an idea is offered: An idea, in contrast to a muscular movement, is the product of neural activity without a recognizable, intrinsic, fixed end-organ of special structure.

Some of the evidences on which the concept of a neurointellectual system is based will be briefly reviewed; this system will be compared with the two other main parts of the central nervous system. For the sake of simplicity, comparisons will usually be made only between the neurointellectual and the neuromotor system, but in each case a similar relationship to the neurosensory system is implied.

This study was supported by the Fund for Research, Inc.

From the Neurological Service of Dr. I. S. Wechsler, the Mount Sinai Hospital. (Dr. Barnum did his work on this paper independently of the Mount Sinai Hospital, with which he was not associated.)

1. Cobb, S.: Emotions and Clinical Medicine, New York, W. W. Norton & Company, Inc., 1950.

2. Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man: A Clinical Study of Localization of Function, New York, The Macmillan Company, 1950.

REVIEW OF EVIDENCES FOR NEUROINTELLECTUAL SYSTEM

Forced Thinking.—By "forced thinking" (*Zwangsdenken,* as used by Steiner [3]) we mean the presentation of thoughts in consciousness, out of context, without the will or control of the subject. The term has not been used much; Penfield, and also one of us (R. M. B.) has stressed it recently.

A. In Epilepsy: Forced thinking may occur in epilepsy, certainly in the presence of lesions, and possibly without them. The epileptic precipitation of thoughts preceding, following, or otherwise mixed with the muscular convulsions has been known since Jackson,[4] Mercier,[5] and Savage [5] first described it. It occurs notably when lesions involve the temporal lobe. The muscular seizures are often preceded by thoughts of jingles, songs, and stories. Attacks of panoramic memory in cases of temporal-lobe lesion are also illustrative, though rare.

The term "forced thinking" has the advantage of linking the events with ordinary convulsions in a systematic fashion, something not accomplished by terms like "epileptic equivalent." The forced ideas are motor equivalents, not epileptic equivalents.

Additional cases have been reported more recently in which the intellectual and emotional phenomena replaced or alternated with the muscular seizure, instead of being mixed with it.[6]

A well-educated professional man, aged 77, with a condition diagnosed as cerebral arteriosclerosis, had attacks in which extremely disturbing thoughts streamed through his mind: "Don't get into that bathtub, you'll drown!"; "Be careful, or you'll fall down those stairs!"; "Don't go to the subway station, or you'll fall in front of the train!" The attacks would arise and terminate suddenly. The thoughts carried no conviction and no affect proportional to the terrible nature of the ideas themselves. There was no urge to act upon them.

Of special interest was the patient's own attitude toward the episodes. He knew his symptoms were really attacks of thoughts, and he usually referred to them in that way. He said "with the rest of my brain I argue with these thoughts, but they always win." Because of these defeats, he coined the phrase, "My brain is smarter than I am." Despite this viewpoint, occasionally he slipped into the terminology of "The voice said . . ." to describe the symptoms.

How often may patients of less intellectual capacity, suffering from similar disorders, lead the physician to believe they really are experiencing auditory hallucinations? One's own thoughts, activated by a pathological process which is external to the normal process of neural association, might readily seem to be spoken by an external voice. In other words, the differentiation of forced thoughts and auditory hallucinations may perhaps be beclouded by the patient's own attitude and his degree of education and of superstition. This very patient, for that matter, may have been having auditory hallucinations, described in such a way as to fool the examiner, although the total body of description, as well as the details, speak strongly against such an interpretation.

3. Steiner, G.: Was lehrt uns die Encephalitis lethargica? Jahresk. ärztl. Fortbild. **18**:5-29, 1927.

4. Jackson, J. Hughlings: Selected Writings, edited by James Taylor, London, Hodder & Stoughton, 1931.

5. Cited by Jackson.[4]

6. Brickner, R. M.: An Aspect of the Physiology of Intellect, Illustrated by Jacksonian Seizures, Bull. Neurol. Inst. New York **7**:245-259, 1938.

Clinically, such disorders as these may sometimes bear resemblances to psychogenic obsessive states, but the sudden onset of the attack and its equally sudden cessation, as well as the usually abnormal electroencephalographic record, suggest a physiological or pathological mechanism of activation or release which can operate on intellectual neurones. By so operating, it identifies those neurones as discrete, real units.[6] Penfield,[7] speaking of intellectual auras, suggests a possible frontal localization, and more recently he has emphasized the temporal-lobe aspects of this phenomenon.

The suggestion from all these cases is that thoughts, like movements or sensations, can appear as forced phenomena, following the physiological or pathological activation of discrete neurone beds.

B. With Electrical Stimulation: Penfield has caused the activation of thoughts by electrical stimulation of areas on the surface of the temporal lobe. His work suggests that specific chains of thought may be activated by stimulation of different, highly localized, small areas. The examples are too many to be reviewed here; the observations are unique, and they should be studied in the original.[8]

C. In Postencephalitic Oculogyric Crises: An opportunity to visualize the reality of specific neurones of intellect and their similarity to neuromuscular neurones is sometimes afforded by patients with postencephalitic oculogyric crises.[9]

Iteration of thought sometimes occurs simultaneously with iteration of muscular contraction during such attacks. The intellectual phase may also precede the ocular phase, ceasing or changing its form abruptly as the ocular fixation comes on. Patients report that their thoughts seem to stand still and remain concentrated on a single item, sometimes for several hours, throughout the whole crisis. Many examples are recorded, ranging from the simplest to extremely complex intellectual, and also, apparently, emotional, states. A simple case is that of Stern's; the patient said that just prior to the appearance of her ocular symptoms her thoughts "stood still," concentrated on a single item, such as why the *O* is round, or how glass making or the written alphabet was invented. It was beyond her power to dislodge the thoughts. In accompaniment there was a "terrible feeling."[10]

The fact that intellectual function is affected in the same way as motor function is strong evidence for the existence of a neurointellectual system, subject to an influence which also affects the neuromuscular system. The same thing happens to the neurones of both systems; the same mechanism dominates them both.

7. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 134.

8. Penfield and Rasmussen,[2] Chap. 9.

9. Jelliffe, S. E.: Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis, New York, Nervous and Mental Disease Monograph Series No. 55, Washington, Nervous and Mental Disease Publishing Company, 1932. Brickner, R. M.; Rosner, A. A., and Munro, R.: Physiological Aspects of the Obsessive State, Psychosom. Med. **2**:369-383, 1940.

10. Stern, F.: Die epidemische Encephalitis, Berlin, Springer-Verlag, 1922; Ed. 2, Berlin, Springer-Verlag, 1928; Über psychische Zwangsvorgänge und ihre Entstehung bei encephalitischen Blickkrämpfen' mit Bemerkungen über die Genese der encephalitischen Blickkrämpfe, Arch. Psychiat. **81**:522-560, 1927.

Speculation concerning the mechanisms involved in such situations suggests the possible role of the closed circuits postulated by Kubie,[11] for the existence of which Lorente de Nó first [12] presented objective evidence. If these circuits are the mechanism, the probability is that many circuits which are not ordinarily closed become closed, or that all ordinarily nonclosed circuits go out of operation. Another possibility rests upon a certain area on the mesial side of the left hemisphere, described by one of us (R. M. B.) [13] and confirmed by Penfield.[14] Electrical stimulation of this area causes a halt in the flow of speech, with continued repetition of the sound which was being made at the moment stimulation began. The repetitive aspect deserves emphasis. Conceivably, this area, or others with like functions, are activated during an oculogyric crisis and are responsible for part or all of the symptoms. Some authors have seen the disturbance of thought as evidence that the whole oculogyric crisis is psychogenic. Among our reasons for believing that a summary of the evidences for a neurointellectual system was indicated is the existence of that approach, with which we must disagree. According to this approach, the occurrence of intellectual or emotional symptoms should remove one's attention from the neural substructure, and even deprive the muscular symptoms of a physiological origin. In our opinion, this type of approach retards understanding of the neurophysiology of behavior, and encourages the development of schools of psychology in which feelings and thinking are by definition unlinked to anything physiological.

Isolated Loss of Specific Thoughts in Hypnosis.—An opportunity provided by Erickson has provided evidence of a somewhat different type concerning the actuality of the neurointellectual system.[15] A subject aged 19 was instructed under hypnosis to forget his age. It was found that in the posthypnotic state he had lost not only the knowledge of number 19, but also the knowledge of its component parts, *1* and *9*. Knowledge of *1* was soon regained, but loss of *9* persisted long enough for many observations to be made. Many derivations of the concept *9* were lost, to the great confusion of the patient when he was confronted with the need for knowledge of *9*. The subject knew something was wrong when he tried to count, read the calendar, etc.; but he was at a loss to determine what it was.

It was thought that, by throwing specific thoughts out of action, the hypnotic process had demonstrated the existence of specific neural networks for those thoughts. Accompanying the presentation of this case was the comment [15]:

> We can also discern the actual, neural reality of some of the ideational components of a total idea. When the neural bed which the patient had to use to think of his age, 19, was thrown out of action, the beds needed to think of the two numbers, 1 and 9, were similarly thrown out. This fact shows, in this particular case, the close anatomical association between the neurone beds for the numbers 1 and 9, and the total concepts "nineteen" and "age nineteen." [Yet] 1 and 9 rested upon two distinct anatomical settings, because 1 returned to function long before 9 did.

11. Kubie, L. S.: A Theoretical Application to Some Neurological Problems of the Properties of Excitation Waves Which Move in Closed Circuits, Brain **53**:166-177, 1930.

12. Lorente de Nó, R.: Vestibulo-Ocular Reflex Arc, Arch. Neurol. & Psychiat. **30**:245-291, 1933.

13. Brickner, R. M.: A Human Cortical Area Producing Repetitive Phenomena When Stimulated, J. Neurophysiol. **3**:128-130, 1940.

14. Penfield and Rasmussen,[2] p. 91.

15. Erickson, M. H., and Brickner, R. M.: Hypnotic Investigation of Psychosomatic Phenomena: The Development of Aphasia-Like Reactions from Hypnotically Induced Amnesias: Experimental Observations and Detailed Case Report, Psychosom. Med. **5**:59-66, 1943.

The situation may be the reverse of Penfield's observations referred to above; by differential stimulation of various temporal-lobe areas, quite specific thoughts were differentially activated, instead of deactivated.

A common experience in hypnosis is the isolated loss of knowledge of the subject's name, address, etc., at the command of the hypnotist. It is believed that all other knowledge is retained, however.

THOUGHT AS A DISTINCT SENSORY FUNCTION, AFFERENT TO CONSCIOUSNESS

If a neurointellectual system does exist, it should have a definite, systematic relationship to the rest of the central nervous system. More specifically, it should be related to the neuromuscular and neurosensory system in a definite, nonmysterious, ordinary fashion.

We suggest the hypothesis that the neurointellectual system is actually an extension of the neurosensory system and that thought behaves as though it were a form of sensation, quite comparable to other forms of sensation.

Discussion of this matter should start by a consideration of the relation of thought to consciousness.

Customarily, consciousness and thought are considered as identical. Actually, there is no more reason to consider thought as identical with consciousness than to consider vision identical with consciousness. One is conscious *of* vision, and of other forms of sensation. One may say that loss of vision deprives one of a certain amount of one's consciousness, but doing so does not advance one's understanding of things. The idea that vision *reaches* consciousness is more helpful. One can analyze vision and its disturbances much more usefully in this way; if one had to take consciousness into account, with all its unknown aspects, one's knowledge of scotomas would be much less clear than it is now.

A study of thought in like fashion—as something not identical with consciousness but as something which reaches consciousness—also proves helpful. It may be noted that none of the evidence touched upon in the foregoing review is necessarily concerned with consciousness, but that it is concerned only with the process of thought per se.

One feels thoughts; one aware *of* them; this is well illustrated by the familiar tip-of-tongue phenomenon, in which one distinctly feels the presence of a thought, and by that feeling knows that it is present, although it cannot specifically be identified at the moment. In this instance the existence and presence of the thought have reached consciousness, whereas the thought itself has not; the thought itself usually also reaches consciousness a little later.

This conception is less radical or far-fetched than it might seem at first blush. A long-standing part of our regular working belief has been that thoughts have a sensory origin; the integrations which begin in the secondary sensory zones of the cortex are already more idea than sensation. Further integrations become more and more idea and less and less pure sensation. Hence, when we describe thought itself as behaving like a form of sensation, saying that it reaches consciousness just as a pure sensation does, we are treading on traditional neurological ground, to some extent at least. We are merely keeping all the compounded integrations of sensation in line with primary sensation, and are saying that consciousness can be

reached by units at any point in the chain, no matter how simply or complexly integrated they may be. The neurones of thought are afferent to whatever neurones are responsible for consciousness.

All this leads to a comment about traditionally postulated variations in degree of consciousness in animals at various levels of the evolutionary scale. The difference between one form and another may not be in the amount or the acuteness of consciousness. Consciousness as such could be the same in all forms, the difference lying in how much an organism has to be conscious *of*. A 6-year-old boy declared, "I know why horses don't laugh! They don't know what to laugh at."

Reaching consciousness is not all that happens to thoughts produced by the neurons of intellect. They may never reach consciousness at all. Whether they do or not, consequences ensue. Motor action (somatic or autonomic) may occur, or additional thoughts may be activated.

This whole hypothesis has been found useful in interpreting certain clinical phenomena, both normal and pathological. Once ideas are considered in the light described, namely, not as identical with consciousness, but as something one may become conscious of, it becomes easier to consider intellectual function in alignment with other neural functions.

DISTURBANCE OF THOUGHT VIEWED AS SIMILAR TO DISTURBANCE OF SENSATION

We shall discuss two very common types of thought disturbance. The purpose of doing this is dual: (1) to add body to the idea that thought is a form of sensation, and (2) to start the construction of something we believe is much needed—a system of nomenclature for the disturbances of intellect which will be consonant with the rest of neurological nomenclature. A more complete reclassification of the disturbances of thought will be presented in a later communication.

Agnosis of Thought (Thought Agnosis).[16]—The term covers disturbances of interpretation of one's thoughts.

16. It has been difficult to find a term to cover this topic. Nielsen's terminology (Agnosia, Apraxia, Aphasia, Ed. 2, New York, Paul B. Hoeber, Inc., 1946) is excellent, in our opinion; it represents a strong move to line up the aphasias, apraxias, and agnosias with the rest of neurological terminology; any additions, such as ours, should accord with it. Basically, "agnosia of thought" does this. However, Nielsen, with reason, limits the use of the term "agnosia" to a disturbance of this recognition in the domain of a single modality of sensation. He thinks, for example, that Liepmann "went too far" in employing "agnosia" for his concept "ideational agnosia," for the latter is a disturbance involving more than one form of sensation at a time. Hence, in order to adhere to Nielsen's concepts, we had to find a substitute for "agnosia." We did not want to abandon the word altogether; this would have been more confusing and disturbing to the settlement Nielsen reached than the out-and-out choice of "agnosia," which, after all, would only extend and not basically vary, the Nielsen structure. "Agnosia" is close to the ideal term for our purposes (α, negation; γνῶσις, knowledge [Hinsie, L. E., and Shatsky, J.: Psychiatric Dictionary, with Encyclopedic Treatment of Modern Terms, New York, Oxford University Press, 1940]), and we need a term denoting loss of knowledge. There is precedent for the wider meaning of "agnosia" (Liepmann, H.: Über die agnostischen Störungen, Neurol. Centralbl. **27**:609-617, 1908. Wilson, S. A. K.: An Introduction to the Study of Aphasia, Lancet **2**:1143-1147, 1921). The use of the term to cover ideas would also be at variance with the usage employed by most authors; ordinarily, it is used to denote loss of knowledge of objects; yet Wechsler (A Textbook of Clinical Neurology, with an Introduction to the History of Neurology, Ed. 4, Philadelphia, W. B. Saunders Company, 1939, p. 348), discussing sensory apraxia, says "the idea of movement is lost, there is agnosia."

(Footnote continued on next page)

The customary modalities of sensation are all subject to disturbances of agnostic type. All may suffer impairments of cortical recognition or interpretation. These include phenomena like astereognosis and the visual and auditory agnosias. Once thought is pictured as an extension of the sensory system, some of its disturbances readily fall into the same type of category.

Thought agnosis is a disturbance in which ideas reach conciousness but are misinterpreted, just as in the sensory agnosias. In the category are a host of disturbances, such as those involving identification of self and others, knowledge of the patient's (and others') place in space and time, and many of the confusional states. We shall exemplify only a few, since they are everyday conditions, well known to all.

A good example is the case of A. P., who wrongly identified the resident, whom she had seen many times before, as "Ellis," an old friend. The resident reached her consciousness by vision, hearing, and touch, just as a test object might; she saw and heard him and felt his jacket and hand. Had the resident actually been defined as a test object, the patient's misinterpretation would have been called visual or auditory agnosia or astereognosis.

Disturbances in concepts of time may be regarded in the same way. When asked what year it is, patients with agnosis of thought commonly end with the conception of being in another life era altogether, and the timing of events within that era is also disturbed. A. P., seen in 1948, said on being questioned that it was "1920, about five years after the war." The test object of time placement was misinterpreted, just as the resident was.

An instance is that of a man aged 50 (a patient of Dr. Charles McKendrie, seen in the service of Dr. Henry A. Riley at the Neurological Institute, New York), who recognized his wife as someone with whom he was intimately acquainted, but not his wife. He said, "I know her well, but I can't place her." Asked if she were his wife, he responded: "She can't be my wife. I'm only 23 now, and I wasn't married till I was 27." At autopsy, scattered intracranial tuberculomas were found.

Patients may show spatial disorientation in a similar way.

Our point is that intellectual disturbances of this kind are fundamentally identical with sensory agnosias, neurologically speaking.

The ideational apraxia of Liepmann belongs in this category. When such states are classified under the single concept of agnosis of thought, they fall into line with other, better understood disturbances, and with ordinary neurological thinking and nomenclature. This is a real gain, for it disposes of the innumerable terms employed for intellectual disturbances, most of which are more social than neurological, and which therefore fail to add to neurological understanding.

After carefully considering all these aspects of the matter in a conference with Nielsen, we chose "agnosis," a variant of the word "agnosia."

The "of thought" part of the definition is also troublesome, not being in strict and euphonious accord with ordinary usage. The only other term which would express our meaning is "ideational." We could not employ this because Liepmann had already used it for different purposes. It is indeed possible that Liepmann had in mind loss of knowledge of ideas as such, independently of sensation in the ordinary sense. However, his concept, as described, is rooted in primary sensation, rather than intellect.

Irreminiscence of Thought.—(This term is comparable to Nielsen's terms "irreminiscence, auditory" and "irreminiscence, visual, verbal." [17]) Ordinarily, this would be called amnesia; we believe the concept of "irreminiscence" is an improvement because it helps to correlate the phenomenon with the rest of neurology.

A. With a Brain Not Grossly Diseased, But Presumably Physically Normal: The term signifies inability to bring to consciousness a thought which is nonetheless present. Probably the commonest form is the ordinary inability to bring to consciousness a thought which is "on the tip of the tongue," mentioned above. This is an ordinary and "normal" experience; yet, still in the absence of gross physical disease, its occurrence is markedly enhanced by fatigue, alcohol, and depressing drugs. In this way, the neurointellectual apparatus again shows a likeness to the rest of the sensory domain; auditory and visual reminiscence, for example, are certainly greatly affected by these factors.

Another common instance is the inability to recall at one time thoughts or words which are readily recalled at another. The fact that they can be recalled at another time is proof that the situation is one of irreminiscence, and not loss.

Hysterical "amnesia" furnishes another example, when the memories which cannot be brought to consciousness to be perceived may be proved to exist by hypnosis.

B. With a Grossly Physically Abnormal Brain: Irreminiscence of thought is seen with tumors, degenerations, intoxications, and probably every variety of pathological state. It is a marked extension of the phenomenon, just mentioned, which happens so frequently to grossly "normal" persons. Here, it is the consequence of destruction of neurones, and not of a mere functional variation of grossly normal neurones. One is more accustomed to detecting this pathological state of things in aphasia and apraxia than in the strictly intellectual sphere; aphasic and apractic patients frequently can express or do at one time things they cannot at another. However, it is very common in the intellectual domain.

This is the condition seen conspicuously in slightly and moderately advanced senility, which ordinarily goes by the more inclusive, less physiological general name of memory impairment. A reasonable explanation would seem to be that, although at least some of the networks underlying the ideas in question may be intact (or the ideas would never be brought to consciousness at all), they cannot always be activated because of damage to other, associated networks, the latter constituting the channels by which the former are normally reached.

Cases can be imagined in which enough of the networks underlying a given idea are intact, but the idea itself is wholly unavailable because the associated networks are so extensively damaged that no activation is possible. In such a case the preserved networks would be an isolated island, and the patient would be as agnostic for the idea as though its underlying neurones were themselves destroyed.

In our present terms, Ribot's law of impairment of recent memory with preservation of memory for relatively remote ideas may be partly explained by the amount of functional linkage a given network of cells (*A*) has with other networks (*B*, *C*, etc.) that can activate *A*. If *A* has been devoted to a given thought, such as that of

17. Nielsen, J. M.: Agnosia, Apraxia, Aphasia, Ed. 2, New York, Paul B. Hoeber, Inc., 1946.

a flag-raising ceremony, for a total of one hour, fewer functional linkages will be formed between *A* and *B* than if the total were 200 hours. The difference results supposedly from the greater or less frequency with which other thoughts have been in action in association with those of *A*. The more of those associated thoughts there were, and the oftener they were activated in association with those of *A*, the more functional linkages there would be between *A* and the associated networks (*B*, *C*, etc.). The more associated units there are (*B*, *C*, etc.), the more can be lost without the possibility being removed of *A*'s being activated by association. The fewer there are the fewer can be spared by *A*; if *A* has functioned in association with other networks only twice, there may be very few such networks, and in widespread pathological involvement of the cortex these few might well be among those lost. In that event, the thoughts of *A* could no longer be evoked by association.

We suggest, as a possible extension of Ribot's law, that rarely evoked ideas may belong with recently acquired ones. Both, supposedly, are highly susceptible to being lost, and presumably for the same reasons.

SUMMARY

1. Some of the evidences underlying the concept of a neurointellectual system are briefly reviewed.

2. The relations of the neurointellectual, the neuromotor, and the neurosensory systems are discussed. Thought is considered as afferent to consciousness, and not to be identical with it, as is often believed. The neurointellectual system is regarded as an extension of the neurosensory system.

3. Some of the disorders of thought are considered on the basis of the concept that thought is an extension of sensation. These thought disturbances, classified in the same way as cortical sensory disturbances, are described as (1) thought agnosis, an inability to interpret correctly those units of thought which reach consciousness, and (2) irreminiscence of thought, an inability to bring to consciousness a thought which is nonetheless present.

Nielsen's basis of terminology is employed. Thus, these particular disorders of thought are brought into closer consonance with the rest of neurology than heretofore. A more complete reclassification of disorders of thought will be attempted in another communication.

CONGENITAL PAPILLOMA OF CHOROID PLEXUS

Report of a Case, with Observations on Pathogenesis of Associated Hydrocephalus

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CHOROIDAL papillomas are of general interest because of their combined pathologic and physiologic implications. As in the case included in this report, through such papillomas evidence may be afforded as to the pathogenesis of the associated hydrocephalus.

Since the survey of 86 cases by Posey [1] 22 additional cases of choroidal papilloma have been reported.[2] The earliest report, by Van Wagenen,[3] of 33 cases, indicated a high incidence in the younger age groups. The fourth ventricle was predominantly the location both in the older patients and in the over-all series, but the lateral ventricles were the usual site in the very young. Posey's survey and subsequent reports have made little alteration in these statistical results.

In the most recently reported series [2d,f] the average age has been somewhat higher. In one series [2f] the predominant location was the fourth ventricle. In the other [2d] the commonest location was a lateral ventricle.

In the case which we report the papilloma, located in the right lateral ventricle, must have been present at birth. Its congenital origin is clearly indicated by the clinical course. The only other apparently congenital papilloma which has been reported is that by Drucker.[4]

From the Department of Pathology, University of Michigan.

1. Posey, L. C.: Papilloma of the Choroid Plexus: Report of a Case and Summary of Recorded Cases, Arch. Path. **34**:911-916 (Nov.) 1942.

2. (*a*) Gerebtzoff, M. A., and Nizet, E.: Étude histopathologique d'un papillome kystique du plexus choroïde du troisième ventricule, Acta neurol. et psychiat. belg. **49**:453-466 (July) 1949. (*b*) Walker, J. C., and Horrax, G.: Papilloma of Choroid Plexus with Report of Unusual Case, J. Neurosurg. **4**:387-391 (July) 1947. (*c*) Sourander, P.: Case of Hydrocephalus in Infancy Caused by Choroid Papilloma, Ann. med. int. Fenniae **36**:679-686, 1947. (*d*) Zander, E.: 6 Fälle von Papillomen des Plexus chorioideus, Monatsschr. Psychiat. u. Neurol. **118**:321-363 (Dec.) 1949. (*e*) Berger, M.: Metastasierendes Papillom des Plexus chorioideus ventriculi IV, Zentralbl. allg. Path. **80**:5-9 (Nov. 2) 1942. (*f*) Ringertz, N., and Reymond, A.: Ependymomas and Choroid Plexus Papillomas, J. Neuropath. & Exper. Neurol. **8**:355-380 (Oct.) 1949. (*g*) Vraa-Jensen, G.: Papilloma of the Choroid Plexus with Pulmonary Metastases, Acta psychiat. et neurol. **25**:299-306, 1950.

3. Van Wagenen, W. P.: Papillomas of the Choroid Plexus, Arch. Surg. **20**:199-231 (Feb.) 1930.

4. Drucker, G. A.: Papillary Tumor of the Choroid Plexus in a Newborn Infant, Arch. Path. **28**:390-395 (Sept.) 1939.

Ringertz and Reymond [2f] were unable to find the mucin mentioned by Globus and Kuhlenbeck [5] and Kernohan and Fletcher-Kernohan.[6] Mucin was not present in our case. Blepharoplasts were absent.

An important feature of about one-half the cases of choroidal papilloma is the presence of hydrocephalus.[1] The pathogenesis of this hydrocephalus is disputed, a fact which is intimately linked to the general argument concerning the mode of production of the cerebrospinal fluid. It is not the purpose of this paper to enter actively into this controversy. Since the choroid ablation experiments of Dandy,[7] it has been assumed that the choroid plexus produces the fluid by a process of filtration [8] or of secretion.[9] A dissenting view is that of Hassin.[10] The proponents of the hypothesis of formation by the choroid plexus appear to be in the ascendancy at present. The case to be reported is in support of that concept.

REPORT OF CASE

J. C., a white boy, was born Sept. 21, 1951, after a short labor. The mother, aged 20, had had three pregnancies, her previous children having been normal. Delivery was normal, with no history of trauma. The child weighed 8 lb. 4 oz. (3,742 gm.) at birth, and was noted to have talipes equinovarus, for which plaster casts were applied.

Shortly after birth, while on breast feeding, the child exhibited an eczematoid dermatitis. This subsided when formula feeding was substituted. The infant apparently did poorly from the beginning, taking only small quantities of the formula. On Oct. 11 there was forceful vomiting during each feeding. The child soon stopped eating and began to have episodes of cyanosis. The parents took him to a local hospital, and it was noted that the head was enlarged. A roentgenogram of the chest revealed nothing abnormal, but x-ray studies of the skull suggested hydrocephalus. He was given oxygen and was admitted to University Hospital on Oct. 14.

On admission the temperature was 99 F., the pulse rate 108, and the respiration rate, 32, per minute. The circumference of the head was 16 in. (40.6 cm.), and that of the chest, 13 in. (33 cm.), and the body length was 20½ in. (52 cm.). The cry was weak, but cyanosis was not noted. The pertinent physical findings were widely open fontanels and suture lines; a large, symmetrical head and small face; long brow, with prominent scalp veins; no tension of the fontanels or suture lines; a poor Moro reflex; poor head control, and left talipes equinovarus. The clinical impression of congenital hydrocephalus was confirmed by roentgenograms of the skull and by a ventriculogram, but these procedures did not suggest a cause. Laboratory studies showed moderate polycythemia and normal urine. The ventricular fluid gave a count of 900 cells per cubic millimeter before, and 320 cells after, the use of acetic acid.

While in the hospital there was progressive afebrile deterioration, with no oral feeding and increasing cyanosis. Death occurred on Oct. 26, 1951.

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5. Globus, J. H., and Kuhlenbeck, H.: The Subependymal Cell Plate (Matrix) and Its Relationship to Brain Tumors of Ependymal Type, J. Neuropath. & Exper. Neurol. **3**:1-35 (Jan.) 1944.

6. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas: A Study of 109 Cases, A. Res. Nerv. & Ment. Dis., Proc. **16**:182-209, 1935.

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8. Fremont-Smith, F.: The Nature of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317-331 (March) 1927. Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H.; Carroll, M. P., and Thomas, G. W.: Equilibrium Between Cerebrospinal Fluid and Blood Plasma: Composition of the Human Cerebrospinal Fluid and Blood Plasma, ibid. **25**:1271-1289 (June) 1931.

9. Flexner, L. B.: Chemistry and Nature of the Cerebrospinal Fluid, Physiol. Rev. **14**:161-187 (April) 1934.

10. Hassin, G. B.: Cerebrospinal Fluid: Its Origin, Nature and Function, J. Neuropath. & Exper. Neurol. **7**:172-181 (April) 1948.

Necropsy.—The body measured 56 cm. in length and weighed 3,650 gm. The anterior and posterior fontanels were wide-open, and the coronal, sagittal, and lambdoidal sutures were widely separated. The occipitofrontal cranial circumference was 44 cm. Talipes equinovarus was present on the left.

Significant pathologic findings were limited to the head, lungs, serous cavities, and liver.

The skull cap was thin; the dura and dural sinuses were normal, and the inner meninges were thin and delicate. The basal cisterns, including the cisterna magna, showed pronounced dilatation, with clear cerebrospinal fluid, as did, to a less extent, the entire subarachnoid space. The entire cerebrum was symmetrically enlarged. In removal of the brain, the thinned-out cortex ruptured, and a large amount of colorless, clear cerebrospinal fluid, estimated at 25%

Fig. 1.—Inferior surface of the brain stem, showing dilatation of the cisterna magna and the thin, delicate pia.

of the total content, leaked out. The brain measured 15 by 12 by 11 cm. and weighed 560 gm. after the leakage of fluid. The gyri were broadened and flattened; the sulci, shallow.

The pons revealed a peculiar, atrophic deformity, with the pontine substance shaped like an upright V. The cerebellum exhibited excavation and atrophy of the medial and inferior surfaces of both hemispheres, with corresponding dilatation of the cisterna magna (Fig. 1). The fourth ventricle was widely dilated; the lateral recesses were widely spread, and the roof was incomplete, with wide opening into the subarachnoid space, the edges of which were covered by atrophic choroid plexus.

On section of the hemispheres, the usual indistinct line of demarcation between the cortex and the white matter of the infant brain was noted. The ventricles were widely and symmetrically

dilated, and the cerebral substance was edematous and extremely thinned, the maximum thickness being 1.5 cm., in the parietal areas, and the minimum, only a few millimeters, in the temporal lobes. The ependymal lining was smooth, and the foramina of Monro were widely dilated, measuring 1 cm. in diameter. The third ventricle was dilated, as were the aqueduct of Sylvius and the fourth ventricle. The ependymal lining here was uniformly smooth and thin. The basal ganglia showed moderate atrophy.

The choroid plexus of the left lateral ventricle and that of the third ventricle were normal. Occupying the position of the choroid plexus of the right lateral ventricle was a large, papilliferous, purplish-brown tumor of great vascularity (Fig. 2). This measured 4.5 by 3.5 by 2.5 cm. Normal-appearing choroid plexus coursed over its superior surface. The tumor was attached to the ependymal surface at its anterior end but was nowhere else adherent or invasive.

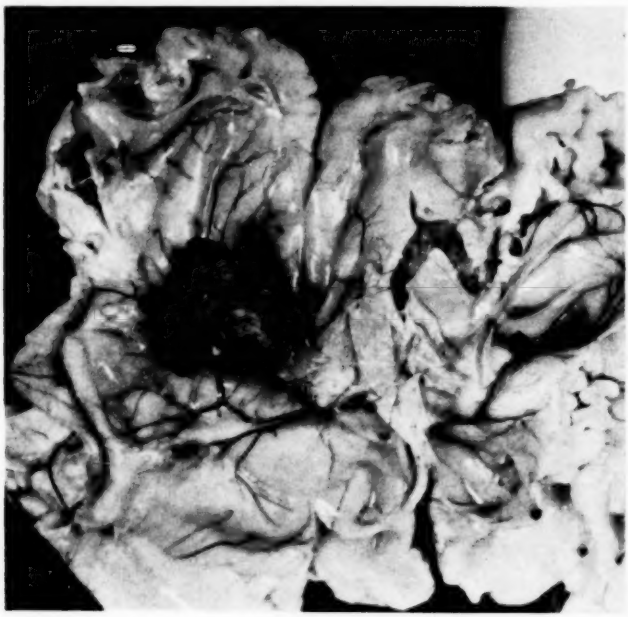

Fig. 2.—Neoplasm *in situ* in the right lateral ventricle.

The base of the skull and the remainder of the skull contents were normal. Petechial hemorrhages into the serous membranes of the thoracic cavity and the mucosa of the gastrointestinal tract were noted. There were scattered areas of atelectasis in both lungs and considerable lipidosis of the liver. Otherwise, necropsy revealed no significant abnormalities.

Microscopic Study: Multiple sections of the tumor, stained by the usual methods, showed it to be composed of papillary formations, consisting of cuboidal cells arranged around a central core of loose connective tissue and vascular spaces (Fig. 3). The cells were fairly uniform in size and shape but varied in density of nuclear staining. The nuclei were finely vesicular, with a few large chromatin granules, but the nucleolus was not prominent. The cytoplasm was somewhat granular and eosinophilic, and in some areas the border was concavely irregular, suggesting ruptured secretory vacuoles. The mucicarmine stain, however, demonstrated no intracellular mucin. Mitotic activity was not noted, and there was no evidence of invasion. Much of the tumor was necrotic.

Sections of the brain showed preservation of the architectural pattern of the cortex and white matter. The subarachnoid space contained a few gitter cells and lymphocytes. One area showed fibroblastic activity with early organization. Many of the oligodendrocytes were swollen. The ependymal lining of the ventricles was frequently interrupted by small glial nodes, which replaced the denuded areas and protruded into the lumen. Glial activity in the subependymal layer was not unusual. The aqueduct of Sylvius was patent.

COMMENT

While we cannot prove, on morphologic grounds alone, that the excess of cerebrospinal fluid present in this case was due only to the existence of a large choroidal papilloma in the right lateral ventricle, it is difficult to interpret the findings in any

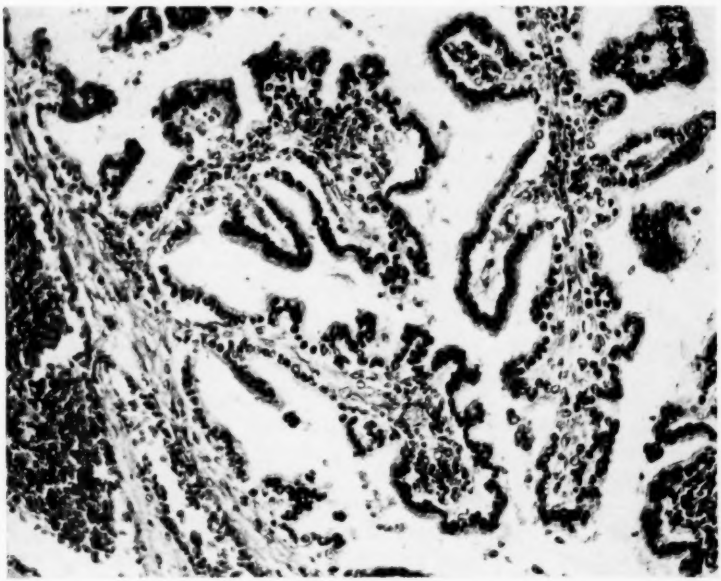

Fig. 3.—Microscopic structure of the neoplasm. There is an orderly arrangement of low columnar or cubical cells upon delicate, vascularized papillae.

other manner. The very great increase in both endothelial and epithelial surfaces resulting from the structure of the neoplasm offers a reasonable explanation for the excess. The absence of any demonstrable block in the pathway further substantiates this view, although we are aware that a functional, or even a mechanical, block during life may not necessarily be manifest at necropsy.

The few cells seen in the subarachnoid space are believed to be the result of the minor trauma incident to diagnostic studies. The glial nodules are attributed to increased pressure within the system, with pressure atrophy of lining cells and replacement by glia.

The absence of ventricular obstruction or significant meningitis in this case appears to support the view that the choroid plexus forms the cerebrospinal fluid

and is capable of causing hydrocephalus by its overproduction, despite the denial of the latter concept by Russell.[11] The major objections to the theory of overproduction hydrocephalus have been (1) the inadequate documentation of recorded cases of papilloma choroideum and diffuse hyperplasia of the choroid plexus, many reports being based on surgical material, and (2) the fact that in most of the reported cases the neoplasm either was located in the roof of the fourth ventricle or was infiltrative, resulting in either case in obstruction of outflow. The present case, by virtue of location of the neoplasm and the information provided by a complete necropsy, offers a reasonably convincing demonstration of the possibility of induction of hydrocephalus by overproduction of cerebrospinal fluid.

SUMMARY

In an infant who died at the age of 35 days, a congenital papilloma choroideum was found in the right lateral ventricle. It seemed reasonable to attribute the accompanying hydrocephalus to overproduction of cerebrospinal fluid, since complete necropsy revealed no cause of obstruction.

11. Russell, D. S.: Observations on the Pathology of Hydrocephalus, Medical Research Council, Special Report Series, No. 265, London, His Majesty's Stationery Office, 1949.

EXOSOMESTHESIA OR DISPLACEMENT OF CUTANEOUS SENSATION INTO EXTRAPERSONAL SPACE

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AMONG phenomena that may be apparent during examination of patients with disease of the sensory pathways is mislocalization of a sensory stimulus. It has long been known that a person with a sensory defect, as seen in the common varieties of cerebral hemiplegia, may inaccurately localize stimuli applied on the paretic side.

Such point mislocalizations are apparent in examinations using a single stimulus and have been described in detail by Head.[1] These mislocalizations can be accentuated by the use of double simultaneous stimulation techniques.[2] In addition, when these techniques of examination are employed, other varieties of mislocalization, such as displacement,[3] become apparent. Displacement is the patterned mislocalization of one of two stimuli simultaneously applied to different body areas. The direction of displacement is in a definite pattern, which is dependent upon the parts of the body stimulated.

Characteristic of mislocalization so far reported has been the fact that their extent was within the limits of the patient's body. In the course of studies of cutaneous perception, we observed a new form of displacement in which the patient consistently and in a predictable fashion mislocalized stimuli into extrapersonal space. This type of displacement we have termed "exosomesthesia." [4]

Exosomesthesia is not a commonly observed phenomenon. More than 400 patients with brain disease were examined at Psychiatric Pavilion of Bellevue

Aided by a Fellowship from the National Foundation for Infantile Paralysis (Dr. Fink).

This investigation was supported in part by research grant #MH-139 from the United States Public Health Service, National Institutes of Health.

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2. Bender, M. B.; Shapiro, M. F., and Schappell, A. W.: Extinction Phenomenon in Hemiplegia, Arch. Neurol. & Psychiat. **62**:717-724 (Dec.) 1949. Bender, M. B.: The Advantages of the Method of Simultaneous Stimulation in the Neurological Examination, M. Clin. North America **32**:755-758 (May) 1948.

3. Bender, M. B.: The Phenomenon of Sensory Displacement, A. M. A. Arch. Neurol. & Psychiat. **65**:607-621 (May) 1951.

4. The term was derived by Dr. Judah A. Joffe (Hinsie, L. E., and Shatzky, J.: Psychiatric Dictionary, New York, Oxford University Press, 1940) from the Greek ἔξω, out of; σῶμα, body, and αἴσθησις, perception by the senses.

Hospital Center by routine and specialized sensory tests. Exosomesthesia was observed in only 15 cases, an incidence of about 3%.[5] The following case reports illustrate the phenomenon and demonstrate some of the conditions under which it was observed.

CASE REPORTS

CASE 1.—H. M., a man aged 64, was admitted to the Psychiatric Pavilion of Bellevue Hospital with a history of progressive mental changes of six years' duration. The first four years of illness were marked by slowly progressive impairment of memory, concentration, and other intellectual functions and by increasing apathy to his environment. In the last two years there was rapid exacerbation of this condition, resulting in the loss of his job as a store manager. During this period his speech became increasingly garbled and stammering. He vacillated between irritability and complete apathy. He was occasionally incontinent, ceased bathing, had difficulty in dressing, and was sometimes so forgetful and confused as to wander into the street without his trousers.

Routine Neurologic Examination.—In walking, the trunk was tilted to the right, and there was a tendency to drag the right lower extremity. However, there was no significant motor weakness, reflex change, or tonus abnormality. Coordination tests were well performed. The cranial nerve functions were intact. Vibration sense was correctly perceived only in the clavicles and the head, while position sense was lost in the fingers, wrists, toes, and ankles bilaterally. Temperature differences were poorly perceived except in the face area. His responses to touch and pinprick stimulation will be described later. A mild degree of "mixed aphasia" was present. This speech difficulty was evident only by special testing or when the patient was fatigued by prolonged examination. There was a fluctuating dyspraxia of moderate severity. Occasionally he had difficulty in dressing, being unable to handle buttons and sleeves. However, he could perform such functions as feeding himself, combing his hair, and other routine daily tasks. He was usually unable to mimic the more complicated patterns of the hand-praxis tests.

An electroencephalogram showed bilateral diffuse abnormality, with decrease in amplitude and intermittent suppression of activity over the parietal regions. A pneumoencephalogram disclosed bilaterally dilated ventricles and moderate "cortical atrophy," particularly in the left temporal lobe.

Psychiatric Status.—Although the patient was oriented for place and situation, he made errors as to date and time of day. There were defects in recent memory, concentration, calculation, and ability to assume the abstract attitude. He usually sat placidly staring into space or wandered aimlessly about the ward. He did not mix with other patients. When approached by members of the staff, he was friendly and passively cooperative. Testing procedures were approached with cheerful indifference. When, however, he was pushed into test situations greater than his capacity, he reacted with increasing irritability and tension, eventually culminating in a "catastrophic reaction." At such times he would become red in the face, shout that he knew the answers but did not want to continue, and suddenly begin to weep.

Body Scheme.—He was able to distinguish the right side of his body from the left, but was unable to make this distinction on the examiner's body. He had no difficulty either in locating midline structures of his body, such as the nose, mouth, chin, umbilicus, and penis, or in pointing to his eyes. With eyes open he readily found both ears; but when his eyes were closed he groped about his face for several seconds before locating them. He could point to his thighs, knees, ankles, and toes but could not point to any specific toe other than the big toe.

He frequently had difficulty in locating portions of his upper extremities. If asked to point to his shoulders, he correctly located one shoulder but then groped behind his neck looking for the other. This defect was even more noticeable in trying to find the "other" elbow and wrist, and greatest in trying to find the "other" hand. His search for the "other" hand or wrist was bizarre. He would look under the pillow or rummage under the mattress, becoming tense and

5. Fink, M.; Green, M., and Bender, M. B.: The Face-Hand Test as a Diagnostic Sign of Organic Mental Syndrome, Neurology **2**:46-58 (Jan.-Feb.) 1952.

insisting it was lost. It should be emphasized that, despite the great difficulty in locating parts of his body, the patient was able to name the body parts, except the fingers and toes. This was true whether the part pointed to was on the patient's or on the examiner's body.

Sensory Status.—(*a*) Single Stimulation: He had difficulty in differentiating between the sharp and the dull end of a pin. This defect was present throughout the body, although he made significantly fewer errors in the face and hands. Touch stimulation was poorly perceived. Usually he could not state whether or not he had been touched. Again, there seemed to be relatively better preservation of this modality in the hands and face.

Except under special conditions of examination of the hands, to be described later, the patient was able to locate the site of a pinprick by pointing. However, if the pin was repetitively and rapidly applied to one region, or if the prick was steadily maintained at that one place, he could not locate the point of stimulation. He would make frantic, random searching movements over his body, and not infrequently around the bedclothes, grimacing as though in pain and exclaiming that he was trying to remove the pin. If asked where he was being pricked, he disregarded the question and continued to try to remove the stimulus. This phenomenon occurred on stimulation of any portion of the body but was most apparent when the hand was tested.

(*b*) Double Simultaneous Stimulation: The phenomena of extinction and displacement were frequently observed in tests of different body areas by simultaneous tactile stimulation. On stimulation of the face and hand, stimuli to the hand were not perceived or were mislocalized to the cheek. In tests of homologous body areas (as hand-hand) extinction of one percept was common. The side on which the stimulus was not perceived fluctuated, so that at one moment only a right-sided stimulus was perceived and a few moments later only a left-sided stimulus was perceived.

Exosomesthesia.—Whenever his palm was in contact with a portion of his body or any other object, and the dorsum of that hand was pricked with a pin, the patient consistently mislocalized the stimulus. This mislocalization was to whatever object the palmar surface of the hand was touching. For example, if the patient's hand was resting on his thigh and the dorsum of the hand was pricked, he insisted that the thigh had been touched, and not the hand. This mislocalization —exosomesthesia—occurred to the thigh, abdomen, leg, or face and was present with stimuli to either hand. It was observed even when the patient was urged to look at the hand during the application of the pin. Exosomesthesia could not be elicited, however, by stimulation of the palm or palmar surface of the fingers when the dorsum of the hand was resting on a portion of the body. Furthermore, localization of stimuli to the dorsum of the hand was correct if the hand was held in space.

Mislocalization also occurred to objects external to his body. If his palm was resting on a table or on his bed, and the dorsum of the hand was pricked with a pin, he would point to these objects and state that the pin had been applied "there." When questioned, he stated that the hand had been touched but continued to point to the bed or table. Frequently, however, he insisted that it was the bed or table that had been touched, and not his hand. If asked how he could feel the bed being pricked with a pin, he would become tense, avoid the question, and insist, "You touched the bed, not me."

Displacement into extrapersonal space was not eliminated by simultaneous stimulation, even when extinction of one of the percepts occurred. For example, if pins were simultaneously applied to the dorsa of the hands while the palms were resting on a table, he would report feeling only one pinprick, that on the left (or right, as dominance fluctuated) and point to the place where the left hand had been resting, saying. "You touched the bed there."

This phenomenon of displacement into extrapersonal space occurred daily during a period of more than two months.

Comment.—In this patient a requisite to displacement into space was that the palm of the hand be in contact with an external object. In other words, there were two cutaneous stimuli simultaneously in operation, namely, the pinprick on the dorsum of the hand and the pressure of the object in contact with the palm or fingers. A single stimulus, such as pricking the dorsum of a hand held in space, did not elicit the displacement.

Exosomesthesia was elicited only on stimulating the hands. This occurred even though single pinprick was perceived more sharply in the hands than in any other area except the face.

Although this patient showed inability to locate correctly parts of his own and the examiner's body, it does not necessarily mean that exosomesthesia is determined by this particular type of disorder in body scheme. The following case illustrates the phenomenon of exosomesthesia in the presence of the patient's ability to locate body parts.

CASE 2.—E. K., a woman aged 52, was admitted to the neurologic service of the Mount Sinai Hospital in August, 1950, with a history of grand mal seizures. She had been in good health until 1947, when there appeared sporadic, momentary sensations of "blacking out." About two years before admission she began to suffer monthly grand mal seizures. There was no aura.

Routine examination on admission showed that her status was within normal limits except for anosmia in the right nostril. There was no organic mental syndrome. X-ray studies revealed evidence of a subfrontal neoplasm. On August 12 a craniotomy was done, and after amputation of a portion of the right frontal lobe, a large bilateral subfrontal meningioma was excised.

Her postoperative course was stormy. For two weeks she was semistuporous. She responded only to massive, painful stimulation, and these responses were limited to vague, ineffective attempts to push away the stimulus. In this period she lapsed several times into coma and showed Cheyne-Stokes respiration. The Babinski response was obtained bilaterally. Her pupils did not react to light.

From about Aug. 23, 1950, the patient improved slowly and steadily. She began to respond verbally, and contact could be maintained for short periods. Vision, which had apparently been absent, began to return, although right homonymous hemianopsia remained for some time. A marked organic mental syndrome characterized by confusion, disorientation, and anosognosia, was present.

Routine Neurologic Examination.—Neurologic examination in September, 1950, disclosed right homonymous hemianopsia, severe impairment of visual acuity with bilateral secondary optic nerve atrophy, nystagmus in all directions of gaze, a bilateral Babinski sign, and a mild degree of aphasia. Position sense, vibration sense, and temperature perception were unimpaired. There were difficulties in perception of touch and pinprick stimuli, as described below.

Psychiatric Status.—The patient was usually friendly and cooperative. However, she was frequently irritable and would not permit examination. She was disoriented as to time and occasionally to situation, but not to place. There were defects in retention and recall, covered by confabulation. She was euphoric and displayed little self-restraint or concern in social situations. Usually she would lie with her body fully exposed. Not infrequently she soiled herself or wet the bed. Anosognosia was prominent.

Body Scheme.—On command, the patient was able to identify and locate correctly parts of her own and the examiner's body, such as the ears, eyes, feet, and parts of the upper extremities. She exhibited some confusion about the right and the left side of the body.

Sensory Status.—(*a*) Single Stimulation: The patient perceived single pinprick stimuli well, although she made occasional nonpatterned errors in localization. These errors were more frequent on the left side.

(*b*) Double Simultaneous Stimulation: On simultaneous application of pinprick to the two sides of the body, except the hands, extinction on the left or displacement on the left toward the level of the right-sided stimulus was the usual response. Homolateral simultaneous stimulation on the right side of the body showed no extinction, but stimulation on the left side elicited frequent extinction and displacement.

Exosomesthesia.—Displacement into extrapersonal space occurred when the left hand was pricked at the same time that either the right hand or the right cheek was stimulated. The phenomenon could also be elicited when the left hand and any other area of the left side of the body were simultaneously stimulated.

Under these conditions the patient mislocalized the stimulus to the left hand into space near that hand, or to the object on which the hand was lying. For example, if pinpricks were

simultaneously applied to the right cheek and the left hand, the patient indicated she had been pricked on the right cheek and the arm of the chair on which her left hand had been resting. As a rule she answered by pointing. If asked to verbalize, she would say, "The right cheek and about here," (pointing to the chair arm or into space near her left hand). If asked directly, "Was your hand touched?" she would avoid the question, responding only, "Here," pointing at the same time to the left chair arm or into space. It is to be noted that, except under the special condition of simultaneous stimulation, the patient was always able to point to or to name her left hand on demand.

If pricked simultaneously on the dorsa of the left and right hands, she correctly localized only the stimulus on the right, both by pointing and by stating, "My right hand." The stimulus on the left, however, was localized only by pointing to the chair arm and saying, "Here." If asked whether the chair arm and not her left hand, had been touched, she answered, "No, here," pointing to the chair arm.

When pinpricks were applied to the left hand and, at the same time, to another area on the left side of the body, a similar displacement into space was evident. Usually the stimulus to the left hand was mislocalized onto whatever structure the hand was resting or else into contiguous space. The other stimulus on the left side was usually correctly localized, though this stimulus, too, was occasionally displaced into space. When this double displacement occurred, the patient would state that she felt two stimuli and would point into space to the left of the arm, stating, "Here and here."

These mislocalizations were repeatedly observed during a period of a month and were not always limited to the left side. They were occasionally observed to occur on the right side. At these times localization on the left was always correct, as indicated by pointing and by verbalization.

Comment.—Exosomesthesia was elicited in this patient only under the condition of multiple simultaneous stimulation. It could not be elicited by single-stimulation methods. Also significant is the fact that exosomesthesia was apparent even though there was no gross disorder in body scheme on routine testing. Furthermore, it is evident that her errors in localization were not simply inability to point to or identify parts of her body by name, as ordinarily she experienced no difficulty in doing this on command.

Both patients mislocalized percepts to parts of the body, to objects, or into space contiguous with the area stimulated. Occasionally, we have also observed displacement of a stimulus to the person of the examiner. Usually such percepts are mislocalized to a homologous portion of the examiner's body; e. g., a stimulus applied to the patient's hand is reported by him as though it had been applied to the examiner's hand. Rarely, the mislocalization is to any part of the examiner's body. This type of displacement is illustrated in the following case.

CASE 3.—R. M., a man aged 52, was admitted to the Psychiatric Pavilion of Bellevue Hospital with the complaint that he had become confused and depressed. For about a year he had been disoriented and confused as to date and his relationship to people and had wandered about the city aimlessly. He had been admitted to the Farm Colony about a half-year before and had worked as a barber until the week before his admission to the hospital.

Routine Neurologic Examination.—Neurologic examination showed normal gait and station. Coordination tests were well performed. The reflexes were active bilaterally, with normal plantar and abdominal responses. Cranial nerve functions were normal. The sensory status showed changes, but only with special methods of testing. A pneumoencephalogram demonstrated moderately dilated ventricles, without shift or deformity, and some dilated cerebral sulci.

Psychiatric Status.—A severe organic mental syndrome was evident. In the ward he sat quietly for hours by his bedside, taking little interest in his surroundings. When approached by members of the staff, he appeared perplexed but was affable. During the testing procedures he was cooperative unless confronted by a test situation in which the examiner demanded tasks

beyond his ability. At such times he showed a "catastrophic" reaction, became excited, and discontinued his efforts in the examination.

He was disoriented for time, place, and situation. However, he was able to find his way about the ward, locating his bed, the nurses' desk, the doctor's office, and the lavatory. Severe difficulties in intellectual function were observed. He was unable to give an adequate history. He could not recall the examiner's name or the events of several hours before but did not confabulate. Calculation and symbol-identification tests were poorly performed.

Severe aphasic difficulties were evident. He was unable to name common objects, clothing, or most parts of the body. He could not comprehend written commands, nor could he write, but he was able to follow simple verbal commands.

Mild dyspraxia was demonstrated in his attempts to imitate finger and mouth movements. However, he was able to dress, feed, and otherwise care for himself.

Body Image.—He had difficulty both in naming body parts and in locating them by pointing. The defects were severest in the fingers, wrists, and elbows, and occasionally the feet. There was difficulty in right-left orientation.

Sensory Status.—(*a*) Single Stimulation: Routine sensory studies of touch, pinprick, and vibration stimuli showed no consistent impairment. These stimuli were usually correctly localized and described. Occasionally a single stimulus to the hand or forearm was displaced to a contiguous object or to space about the upper extremity.

(*b*) Double Simultaneous Stimulation: On double simultaneous [touch] stimulation the patient displayed extinction and displacement of tactile stimuli. This was most evident in trials of the face-hand test [6] but was seen in tests of other body parts as well. For example, on simultaneous stimulation of the cheek and the opposite hand, he would either report only the stimulus to the cheek (extinction of the hand stimulus) or report a stimulus to each cheek (displacement of the hand stimulus). The pattern of sensory dominance was that usually seen in diffuse cerebral disease, the face being most dominant, the hand least.[5] There was no lateral dominance.

Exosomesthesia.—Displacement into extrapersonal space was occasionally observed on single stimulation. This displacement was from the hand, forearm, or elbow to space contiguous to the part touched. Exosomesthesia was, however, markedly exaggerated when double simultaneous stimulation was employed. Again, the areas from which the phenomenon was most frequently observed were the hands, forearms, and elbows. For example, when stimuli were applied to the dorsa of the hands as they were lying on the patient's lap, he pointed to space in front of his knees. If asked to state where he had been touched, he would say, "The hands," but would continue to point to the space in front of his knees. Exosomesthesia was rarely noted when other body parts, such as the cheeks or shoulders, were simultaneously stimulated.

Occasionally it was found that on tests with double simultaneous stimulation the patient mislocalized a stimulus from his body to the homologous region of the examiner's body. For instance, when the hands were simultaneously touched, he would grasp the examiner's hands and affirm he had been touched "there." Despite the examiner's insistence that the stimulus had been to the patient's hands, the patient would persist in pointing to the examiner's hands. When asked to name the parts touched, he would say "There, there." The same phenomenon was occasionally observed on simultaneous stimulation of the two elbows or cheeks. It was significant that this mislocalization to the examiner's body occurred even when the patient was urged to look at the stimulations.

It was observed that emotional tension, increase in the rate of testing or undue prolongation of the examination increased the incidence of exosomesthesia. For example, to initial application of pinprick to the right hand and the left cheek, the patient reported only the face percept, omitting the hand stimulus. Later, he localized the two stimuli to the cheeks. As the examination progressed and the physician speeded up the testing, the patient became tenser. He then localized the face percept correctly but insisted that the hand stimulation was into space in front of the hand. Finally, both stimuli were displaced into space or to the examiner's body.

These phenomena were observed daily over a period of 2½ months.

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6. Bender, M. B.; Fink, M., and Green, M.: Patterns in Perception on Simultaneous Tests of Face and Hand, Tr. Am. Neurol. A. **75**:250-252 (June) 1950; Patterns in Perception on Simultaneous Tests of Face and Hand, A. M. A. Arch. Neurol. & Psychiat. **66**:355-262 (Sept.) 1951.

Comment.—While single stimulation occasionally produced exosomesthesia in this patient, the phenomenon was more pronounced under conditions of double simultaneous stimulation. This patient also mislocalized stimuli to the examiner's body. Emotional tension, prolonged examination, or increase in the rate of testing exaggerated the phenomenon of exosomesthesia.

GENERAL COMMENT

On consideration of these cases, it is immediately apparent that exosomesthesia is associated with a severe organic mental syndrome. Therefore, it might be argued that exosomesthesia is merely a manifestation of the patient's mental confusion; that the patient simply points into space because he is confused. However, we have examined many severely confused patients and found exosomesthesia only rarely. Moreover, exosomesthesia is a patterned phenomenon, demonstrable in each patient under defined conditions, predictable as to the area from which it will occur and the extrapersonal spatial region to which the sensation will be projected. For example, in Case 1 exosomesthesia could be elicited only from the hand, and only when the dorsum was stimulated at the same time that the palm or fingers were in contact with another object. Displacement under these circumstances was usually not haphazard. As a rule it occurred to the object touching the palm or fingers. In Case 2 exosomesthesia could be elicited only by double simultaneous stimulation. It was seen most clearly in the hand and could be elicited only unilaterally at any one examination. Again, the displacement was not haphazard; the stimulus as a rule was localized to extrapersonal space contiguous to the area actually stimulated. In Case 3 the phenomenon was observed again under conditions of double simultaneous stimulation, and the displacements were either to space contiguous to the stimulated area or to homologous areas of the examiner's body. It is significant that these displacements could be elicited even when the patient was urged to look at the application of the stimuli. Moreover, even when the examiner pointed out the error in localization and emphasized the implausibility of the response, the patient characteristically insisted on the correctness of the mislocalization.

Factors Influencing Exosomesthesia.—Many factors influence the appearance of exosomesthesia. Except in children under special conditions, it has been observed exclusively in patients with severe mental changes resulting from disease of the brain. It is influenced by the type of stimulus used and the rate of stimulation, as well as by the element of simultaneity of stimuli. Moreover, the emotional state of the patient has a significant effect on the phenomenon, as does the part of the body stimulated. In some cases exosomesthesia has been made apparent by administration of small doses of amobarbital sodium. These factors will be discussed.

(*a*) Bilateral Cerebral Disease: The symptom background in every case of exosomesthesia is an organic mental syndrome secondary to bilateral cerebral disease. We have not been able to demonstrate exosomesthesia in an adult unless there were severe mental changes. But, as previously noted, it is a rare phenomenon, and only a few patients with severe organic mental syndrome show it. In 400 patients with organic cerebral disease, of varying severity, exosomesthesia was observed in approximately 3%.[5] Even in these patients it was not manifest in every examination, and its frequency was readily altered by changes in the conditions of testing. It is therefore evident that severe bilateral cerebral disease in itself is not sufficient to produce exosomesthesia.

(*b*) Effect of Simultaneous Stimuli: That simultaneous stimulation may elicit sensory phenomena not apparent on single stimulation has previously been demonstrated.[2] For example, a hemisensory syndrome in a hemiplegic patient may not be discernible except under conditions of double simultaneous stimulation. Thus, single stimulation may be well perceived and localized by the patient, but the addition of a second stimulus simultaneously applied may so affect integration that the phenomena of extinction, obscuration, and displacement become apparent.

Similarly, simultaneous stimulation elicited exosomesthesia when it was absent on single-stimulus examination, or exaggerated it when it was occasionally manifest on routine stimulation. In Cases 1 and 2 simultaneous stimulation was a necessary condition for eliciting the phenomenon. It could not be demonstrated by single stimulation. In Case 3 exosomesthesia could occasionally be elicited on single stimulation, but with simultaneous stimulation the phenomenon was demonstrated with much greater frequency.

(*c*) Type of Stimulus Most Effective: Of the various stimuli used in these examinations, such as single touch, single pinprick, repetitive touch, and repetitive pinprick, it was noted that repetitive touch stimuli were most effective in eliciting exosomesthesia. This was especially true on double simultaneous stimulation.

(*d*) Effect of the Patient's Emotional State: Exosomesthesia was exaggerated by alterations in the test situation which made performances more difficult. Increasing the rate of stimulation or unduly prolonging the examination increased the displacements to extrapersonal space. If the examiner was deliberately critical of the patient's errors, the phenomenon also appeared with greater frequency. These factors increased the emotional tension of the patient and if carried further produced a "catastrophic" reaction.

(*e*) Effect of Drugs: It has previously been demonstrated that difficulties in perception may be exaggerated by barbiturate intoxicants.[5] Amobarbital sodium was administered intravenously in doses of 3 to 7 grains (0.2 to 0.45 gm.) to patients with diffuse cerebral disease. Prior to administration of the drug, these patients manifested the phenomena of extinction and displacement of percepts on simultaneous tests, but not exosomesthesia. While under the influence of the barbiturate, three patients showed exosomesthesia, in addition to extinction and displacement. In two other patients, in whom exosomesthesia had been elicited only after a protracted testing period, the administration of amobarbital sodium elicited exosomesthesia at the onset of testing and exaggerated the phenomena of extinction and displacement.

Relation of Exosomesthesia to Extinction, Obscuration, and Displacement.—In our experience, whenever exosomesthesia has been observed, the phenomena of extinction, obscuration, and displacement are also present. Exosomesthesia, however, is a rare phenomenon, whereas extinction, obscuration, and displacement are commonly observed. Moreover, whereas extinction, obscuration, and displacement are frequently seen in adult patients with mild cerebral dysfunction,[5] displacement into extrapersonal space is present only in cases of severe mental changes due to disease of the brain. It may therefore be concluded that exosomesthesia in adults represents a severer type of cerebral dysfunction than other simultaneous stimulation phenomena.

Relation of Exosomesthesia to Body Image.—It might be said that exosomesthesia is a pathologic extension of the body image. The normal person is continually extending the boundaries of this image. For example, Head cites the examples of the woman with a feather in her hat who "feels" when the feather is touched, and the surgeon who handles his probe as though it were an extension of his fingers.[1] In the normal person, however, these extensions of the body image are fluid, immediately reversible, and clearly recognized by the subject as artificial. The surgeon, for example, is able at any moment to redefine correctly his body image. He "knows" that the probe is not his finger. In the group of patients described above, however, the extension of the body image seems to operate in a pathologic, rigid form. Under certain conditions these patients lose the ability to maintain a realistic definition of the limits of their body. They behave as though portions of the contiguous external world are concretely incorporated into the inner image of their body's extent.

Although we may consider exosomestheisa as a specialized body-image disturbance, it should be noted that patients who do not show difficulties in identification and location of body parts still may show mislocalization into extrapersonal space. On the other hand, patients with an inability to identify or locate their body parts on command do not necessarily manifest exosomesthesia.

In similar fashion, there is no necessary relationship between exosomesthesia and position-sense difficulties. A patient (Case 3) who manifested displacement of sensation into extrapersonal space did not make errors in routine tests of position sense in the extremities. This is consistent with observations previously made by Head [1] that localization of single stimuli is not functionally related to sense of position of the extremities.

Role of the Hand.—Although displacement into extrapersonal space has been elicited from various areas of the body, it has been observed to occur most frequently from the hand. Moreover, in no case has it been elicited from another area and been absent from the hand.

This predilection for the hand is consistent with the manner in which other dysfunctions of the nervous system are reflected. As a rule, when the functioning of one side of the body is impaired through cerebral disease, the disorder is most manifest in the hand. Thus, in the usual hemiplegia resulting from a capsular lesion the paresis, body-image disturbance, and sensory loss are most prominent in the hand and fingers.

In these patients, and in others with diffuse cerebral disease, the phenomena of extinction, obscuration, and displacement are also best elicited when the hand is tested. Furthermore, studies of the order of sensory dominance of various areas of the body demonstrate that the hand is in the lowest rank. This is true of the dominance order of patients with cerebral disease,[5] and also of normal subjects, both adults and children.[6]

Similarly, when allesthesia is observed, it is seen most clearly in the hand. Bender and Nathanson [7] described a case in which the clinical course was reflected in a

7. Bender, M. B., and Nathanson, M.: Patterns in Allesthesia and Their Relation to Disorder of Body Scheme and Other Sensory Phenomena, Arch. Neurol. & Psychiat. **64**:501-515 (Oct.) 1950.

waxing and waning allesthesia. As this patient improved, the areas from which the phenomenon could be elicited diminished, until finally allesthesia was demonstrable only in the hand.

In autotopagnosia the hands are more profoundly affected than other regions. Finger agnosia, possibly the earliest sign of body-image disturbance, is frequently seen in the absence of other gross disturbances of the body schema. Furthermore, phantom limb, anosognosia, causalgia, and synesthesia are phenomena in which the role of the hand is especially prominent.

Just as these pathologic phenomena are manifest in tests of other body parts, but are most clearly demonstrable in the hand, so, too, exosomesthesia, though occasionally demonstrable elsewhere, is most apparent in examination of the functions of the hand.

Exosomesthesia in the Normal Child.—It has been observed that sensory phenomena which occur in patients with cerebral dysfunction may be found in the normal young child.[8] Similarly, exosomesthesia, which we have never found in adults except when there is severe cerebral disease, can be readily observed in children up to the age of 4 years. In examination of a large series of normal children it was noted that the initial responses of children to double simultaneous stimulation frequently included exosomesthesia, although the commoner responses were extinction and displacement. Exosomesthesia was rare, however, after the initial few trials.

The frequency with which exosomesthesia may be seen in children up to the age of 4 years suggests that it may represent, in the child, a "normal" developmental stage in the organization of perception. Its appearance in adults with severe brain disease may possibly be, as with other pathologic phenomena, a regression in function to a previous level of sensory integration.

SUMMARY

The patterned mislocalization of tactile stimuli into extrapersonal space is described and termed exosomesthesia.

Exosomesthesia is observed in patients with severe organic mental syndromes. It is apparent only rarely on single tactile stimulation and is more readily elicited by the technique of double simultaneous stimulation. It is exaggerated by fatigue, rapid testing, and increased emotional tension. Barbiturate intoxication also may elicit or exaggerate the phenomenon.

Exosomesthesia is most apparent in stimulation of the hand but has been observed in tests of other body parts. While it may be considered a pathologic extension of the body image, it is not dependent upon concomitant body-image disturbances.

Although exosomesthesia has been observed chiefly in patients with severe mental changes, it is not a manifestation of confusion, but is a patterned, predictable phenomenon. It may be a regression, in patients with cerebral dysfunction, to a previously "normal" stage in sensory development, as suggested by the fact that it is readily observed in simultaneous tactile tests of young children.

INSULIN COMA AND GROUP PSYCHOTHERAPY

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THE MATERIAL reported on in this paper was derived from a private mental hospital in which the emphasis on psychiatric treatment centers about the patient's total hospital experience. Such hospital-treatment experience includes the carefully coordinated services of the psychiatric medical staff, social service case work, nursing care, and various forms of group, physical, occupational, horticultural, and recreational therapies. Electroshock and insulin coma treatments are important forms of adjunctive therapy which are used as indicated. We have realized for some time that both electroshock and insulin coma therapy can be most effective only when they are used as parts of the total psychotherapeutic approach to the patient and his illness. Accordingly, the following treatment program is based on two premises. The first is that in the treatment of schizophrenia, insulin coma is the treatment of choice; the second, that treatment is in no way complete unless it includes the psychotherapeutic program. On this basis we feel that we can speak of "insulin coma" and "insulin coma therapy." The latter implies a complete and organized program on a rational basis directed toward a better personality integration of the schizophrenic patient.

The study upon which this paper is based was set up in a private hospital with an average census of 160 patients. The insulin unit could accommodate 15 patients at one time, and during the period in question—October, 1950, to June, 1951—the census ranged from 6 to 15. Two physicians were assigned to the unit, in addition to two graduate nurses and two or three trained male attendants. An average of six student nurses at one time were assigned to the unit for periods of three weeks.

In this way, an attempt was made, with some success, to keep the personnel within the unit relatively stable. As a result, an unusual amount of familiarity and understanding developed among patients and personnel responsible for their care. The average course of insulin coma treatment was of 54 days' duration.

Male and female patients were housed in separate halls. So far as possible, patients on active treatment were kept together when outside the treatment unit, and within the hospital they came to be known as a somewhat unique group.

The fact that insulin therapy is of value cannot be denied, and this program of treatment could not have been formulated without it. Because this therapy provides

From Friends Hospital.
Read before the Insulin Therapists Association, Philadelphia, June 27, 1951.

the opportunity for a greater reintegration of the individual, we see it as being preferable to electroshock therapy. Electroshock, in our minds, seems to produce a temporary disorganization in the thinking capacity of the individual, so that reintegration must take place as the confusion clears. In insulin coma the absence of confusion enables the patient to follow and utilize a connected and rational program of therapy. It is this program which we shall describe in this paper.

In a discussion of psychotherapy and the schizophrenic patient, certain aspects of our concept of the illness must be considered. Some of these, as well as other factors, have been discussed by Lewis [1] in a recent article. Probably the commonest is the tendency to think of schizophrenia in terms of prognosis, and on that basis to allow one's interest to be diverted to other, less discouraging forms of illness. Yet more and more the psychiatric literature contains reports concerning the problems and methods of therapy in psychotic states. Reviews of the over-all problems have been presented by Federn [2] and Betz.[3]

The schizophrenic, in our minds, is a person who is immobilized by ambivalence. This ambivalence affects first his relationships to other people, then himself and his own sexual identification, and, finally, produces total confusion and inability to decide what is real and what is unreal. It is the last factor, namely, the inability to distinguish reality from unreality, that is characteristic of the schizophrenic process. A rational therapy then must be directed toward all the phases of the problem. Insulin coma can be thought of mainly in terms of its helping to bring the patient back to reality and giving him an opportunity to begin to reintegrate himself. At this point the treatment course has been considered by many to be complete. We feel, however, that here treatment has only begun, and that it is necessary through group and individual therapy to help the patient to begin to understand himself and his relationships to other people.

In the treatment of the schizophrenic patient, we feel that group therapy plays a very important part in this reintegration. Several authors have utilized and reported on this technique.[4] An individual's adjustment amounts to his utilization of interpersonal relationships. His problems are most evident in his relationships to other people. The schizophrenic is at a point farthest from a satisfactory relationship and must be looked upon as an infant who must learn first about himself and then about reality, which includes people and how to relate to them.

Reestablishment of such a relationship is dependent upon verbalization and socialization. Group therapy facilitates the attainment of this goal. The ultimate

1. Lewis, N. D. C.: What Do We Know About Dementia Praecox? Ment. Hyg. **34**:569 (Oct.) 1950.

2. Federn, P.: Psychoanalysis of Psychoses: The Psychoanalytic Process, Psychiatric Quart. **17**:470 (July) 1943.

3. Betz, B.: Strategic Conditions in the Psychotherapy of Persons with Schizophrenia, Am. J. Psychiat. **107**:203 (Sept.) 1950.

4. Abrahams, J.: Preliminary Report of an Experience in the Group Psychotherapy of Schizophrenics, Am. J. Psychiat. **104**:613 (April) 1948. Gifford, S., and MacKenzie, J.: A Review of Literature on Group Treatment of Psychoses, Dis. Nerv. System **9**:19 (Jan.) 1948. Klapman, J. W.: Intra-Mural Group Psychotherapy, Illinois M. J. **89**:226 (May) 1946. Lazell, E. W.: The Group Treatment of Dementia Praecox, Psychoanalyt. Rev. **8**:168, 1921. Marsh, L. C.: Group Treatment of the Psychoses by the Psychological Equivalent of the Revival, Ment. Hyg. **15**:328 (April) 1931. Ross, W. D.: Group Psychotherapy with Psychotic Patients and Their Relatives, Am. J. Psychiat. **105**:383 (Nov.) 1948. Wender, H. B.: Experiences in Group Psychotherapy in Insulin-Treated Patients, Psychiatric Quart. **24**:314 (April) 1950.

expression of feelings depends primarily upon the ability to put them into words, a principle which is the basis of psychotherapy. To us, it is important, then, to give the schizophrenic the opportunity to learn to express himself and to hear his own voice before others in a therapeutic setting. From this point, he can progress to the contribution of actual ideas and appropriate remarks, which are commented upon by others. This leads to socialization and a reestablishment of the patient's sense of "belonging." Admittedly, these are the usually understood qualities of group activity; yet the point here is that in the schizophrenic a very minimal response must be considered as being significantly positive, and that one cannot expect, particularly in the early phases of treatment, responses such as might be given by a more normal person. We, accordingly, set up in our program opportunities for the patient to develop these two aspects of verbalization and of socialization. If these are successfully developed, the patient is then in a much better position to be able to take further help on an individual basis or in further group work.

The treatment program might be looked upon as being like a greenhouse, where, under most optimum conditions, seeds are started and early phases of growth are nurtured. Just as the seedling is gradually acclimated to a more rigorous and changing atmosphere, so the schizophrenic patient must be protected, guided, and encouraged as he develops greater ego strength.

PHASES OF TREATMENT

Insulin coma is directed toward bringing the patient back to reality. We believe that this is achieved through two general functions, physiological and psychological.

As far as the physiological functions are concerned, we still lack an adequate explanation of results. In view of the current thinking along the line of the "general adaptation syndrome," [5] it may be that the factor of continual reapplication of stress may function in such a way as to give the individual a greater physiological resilience. Perhaps, on the other hand, this resilience does exist normally, and in most patients who are treatment failures it may be their lack of it that accounts for their inability to change. We might point out here the work of Pincus, Hoagland, and associates,[6] in which the chronic schizophrenic patient was definitely found to be a hyporeactor. There are those who maintain that the effect comes through definite pathophysiological changes; this, however, remains to be substantiated. We might point out that most of the patients we treated had preinsulin and postinsulin psychological examinations. In those patients who received no electroshock there was no evidence of any organic involvement in the psychological patterns. This material will be reported on in detail later. One cannot deny a certain physiological advantage, however, inasmuch as various other drugs used to produce comatose states do not have the same effect on the illness as does insulin.

The psychological functions of insulin coma might be considered as being both direct and indirect. The direct functions are related closely to the coma itself. We believe these actions are very important in restoring to the patient a sense of reality. Daily comas allow the patient to distinguish the constancy of conditions on awaken-

5. Selye, H., and Fortier, C.: Adaptive Reaction to Stress, Psychosom. Med. **12**:149 (May-June) 1950.

6. Pincus, G.; Hoagland, H.; Freeman, H.; Elmadjian, F., and Romanoff, L. P.: A Study of Pituitary-Adrenocortical Function in Normal and Psychotic Men, Psychosom. Med. **11**:74 (March-April) 1949.

ing as being real and his own mental productions as being unreal. On a good number of occasions we have had patients describe to us their experiences on awakening, in which they were aware of recurrent hallucinations only to have them dissolve as they returned to the waking state. The reaction of awakening functions to give the patient a frame of reference in which he can examine the quality of his convictions and distorted perceptions. Another direct psychological function of insulin therapy is one of abreaction. This usually is also a function of the waking periods and the depth of the coma. Many patients experience abreactions in the lighter phases of coma or on awakening, particularly after having been in the deeper stages of coma. Since some abreactions may be recalled by the patient, they have proved valuable in terms of his understanding of himself and in the emotional release accompanying the production of relevant material. Oftener, however, such abreactions do not come to a conscious level after treatment. The release of hostility during treatments is obvious in some patients. Whether or not this functions as a dynamic release, in view of the fact that it may never reach the patient's awareness, is difficult to say.

The indirect psychological functions of insulin are those which are oftenest mentioned, namely, the constant attention, the reassurances, and the detailed personal care which the patient receives. These factors are important and serve to make reality attractive to the patient on awakening. It is our belief that it is the schizophrenic's relationship to and his feelings toward reality which may determine the degree of recovery. He must come to find that reality can be tolerated and that he can master it; otherwise his illness is a much better solution to his emotional needs. It is in this respect that early treatment is so very important. As long as the patient has some memory of objectives that can be attained by living in the outside world and with other people, it is much easier to support him in doing so. However, once his illness has become to him a way of life, treatment efforts serve only to engender greater hostility within him.[1] In the treatment of the neurotic patient, the will to get well and the overcoming of resistance to recovery are important. In a patient who has had to make a schizophrenic type of adjustment these factors play an even greater part. His limited insight into what has happened makes it especially difficult for him to comprehend any directed efforts to change him.

DESCRIPTION OF GROUPS

As indicated before, the insulin group therapy program was devised from the necessity of developing and helping the patient toward better integration. Three types of groups were utilized in this over-all treatment program.

The first type was that of a "discussion" group. Here the patient was oriented to his treatment, given an opportunity to meet the other patients in his unit, and encouraged to discuss common problems.

The second type we chose to call the "picture-stimulus" group. This was to help the patient become more aware of interpersonal problems through the use of a predetermined stimulus to verbalization in a controlled situation.

The third type, considered as a "follow-up" group, served to help the patient in his transition from hospital to home and job.

Each patient while in the insulin unit had two hours a week of group therapy. The orientation group met one hour a week and included all the patients in the unit. Topics most frequently discussed were the nature and purpose of treatment, the length of treatment, the drugs and medicaments used, the problem of secondary

reactions, reactions under treatment, and any other topics relating directly to treatment procedure. An opportunity was afforded here for the patient to express his hostility toward the hospital and his relatives, and to be reassured by the support of the group. An effort was made to answer all questions. Most important, however, in this phase was an opportunity for the therapist to present to the patients the reasons for treatment and to reiterate the necessity for treatment. This served further to reinforce the belief of these patients in their own need of treatment.

Not infrequently patients' recitals would become very inappropriate and rambling. This situation was usually permitted, inasmuch as it was thought that if the patient merely had an opportunity to talk, it was of value to him. Description by one patient of hallucinatory and delusional experiences as components of his illness served to lead other patients to question their own distorted perceptions.

Another rather common topic of discussion was the fear of electroshock treatment, since many of the patients had previously had such treatment. Without exception, the patient who had had a course of electroshock treatment preferred insulin coma. The commonest reasons for fear of electroshock treatment seemed to center about death by electrocution, the power of electricity, the very disturbing confusion produced, and the severe memory loss. Some patients also described the marked anxiety accompanying the seeming loss of behavior control.

After several meetings of the discussion group, problems relative to daily treatment, conduct in the hall, and experiences of their illnesses were somewhat exhausted and the group discussion tended to be somewhat irrelevant as far as subject matter was concerned. In order that the patient might be made more aware of interpersonal relationships, the implications of living with people, and that those patients who had difficulty in verbalization might be stimulated, the picture group was set up. The value of picture stimuli in group therapy has been discussed by Prados.[7] Because of its uniqueness, we shall report here in some detail the experiences with this type of group.

The cartoon drawings of the Rosenzweig Picture-Frustration Study were utilized. These were mounted on cardboard and were projected on a screen. Patients were seated about the screen with the therapist among them. The room was kept in semidarkness, this being a mechanical necessity. The darkened room seemed to stimulate freer expression and to lessen self-consciousness.

A preliminary statement was made to the effect that a series of cards would be used illustrating problems in interpersonal relationships. It was explained that since one's problems concern people and various situations involving people, a much better understanding could be gained by reviewing some of these situations. The patients were then asked to state what they felt was happening in the cartoons and how the person represented would handle the problem. Each patient was given an opportunity to express his ideas, and if he did not spontaneously give a response, he was called upon before the next picture was presented. With such a technique, we found that a good deal of meaningful material was produced. Often a patient would find one or another of the situations pictured to be quite close to his own problem. Another patient would recall similar situations or project himself into the situation illustrated. The patients were amazed by there being so many answers for what seemed to be a fixed situation. Particularly interesting were the viewpoints

7. Prados, M.: The Use of Pictorial Images in Group Therapy, Am. J. Psychotherapy **5**:196 (April) 1951.

of the men as opposed to those of the women. This was illustrated most clearly in the "hostility" cards. Here, a passive male response would often be scorned and questioned by a woman, who felt a man would act in a much more direct manner. It was possible with the series of cards to find those which stimulated much greater discussion, such as sibling rivalry, hostility toward parental figures, feelings of isolation, love and hate, projection, and rationalization.

A set of similar cards was devised to present other topics for discussion, e. g., attitudes toward hospitalization, mental illness, and problems of readjustment. Thus, through these cards a good deal of material for discussion was obtained. An effort was usually made to carry over the discussion ideas from one hour to the next. We feel that some awareness of problems of living with people was obtained through the use of these cards and that the patient was helped to make better use of individual therapy.

The third group consisted of patients who had completed their insulin coma treatments. This follow-up contact served as a further stepping-stone back to reality for the schizophrenic patient. This was particularly true when several patients who had already left the hospital were included among them. During his acute illness and insulin treatment, the patient had been living in a carefully protected and, therefore, not entirely realistic environment (in terms of demands made upon a person in normal living). The discussion and interplay within the group, now past the important milestone of physiological treatment, tended naturally to move toward the problems concomitant with leaving the hospital.

Thrusting the patient from the relatively benign and protected environment of the hospital into the world he had previously found so hostile and traumatic might without support or preparation have overwhelmed the patient who was still anxious and insecure. However, by being able to share his anxieties with his fellows, and finding himself not alone in his feelings, he was often able to gain considerable support from the others in separating from the hospital. This was especially true when one or more of those who had already left the hospital could recount such experiences as the intramural patient could only anticipate. These patients, in turn, found the group of value as a source of support during their early efforts at reestablishing themselves, both through continuation of their identification with the group (and hospital) and from the reassurances gained by observing others who had left and who were able to cope with similar problems. It might well be noted here that the social service case work with significant relatives often did much to help the patient through this difficult transition period.

The first several patients to complete therapy and become the original nucleus of the group fortunately made excellent progress in insulin treatment and very adequate later adjustments, both before and after leaving the hospital. As a result, these people became efficient instruments in alleviating the anxiety of the other patients faced with the ordeal of returning to the outside environment.

This was one of the most obvious beneficial effects noted in this particular group. The patient with some insight into the fact that he had been ill recalled, much to his own discomfort, at least some of his incongruous behavior prior to hospitalization. Naturally, there was a considerable amount of doubt in his mind as to how those with whom he had previously had contact were going to receive him. Not only did he have the effects of his behavior to overcome, but also the very real stigma in the

minds of many people of having been in a mental hospital. There was also the uncertainty of his own ability to return and readjust adequately to situations he had previously considered to be extremely difficult, if not impossible.

The patients in this group usually discussed problems on a very practical level. One of the most important questions to come up was the patient's attitude toward his illness in relation to returning to his job or applying for a new one. A frank acceptance of the fact that he had been ill and needed hospitalization appeared to be one of the most important factors in helping the patient to deal adequately with the problem. The manner in which the patient handled the question of illness in regard to the employer was significant. For example, in four instances in which the patients had done very well in their jobs since discharge all the employers were thoroughly aware of the nature of the patient's illness. Two returned to previous employers, and two went to new jobs.

In such cases it is felt that not only the patient and the employer gain in having a more honest and satisfying relationship, but the patient can usually come to look upon his hospitalization as an aid, rather than an obstacle, to his future progress.

In conjunction with treatment for the patient himself, carefully planned social case work was carried out with the patient's relatives. This consisted in a series of interviews for the relative with one of the members of the social service department of the hospital. Through these collaborative interviews, it was possible to give the significant relative an opportunity to understand the patient's illness and to clarify his own feelings toward the patient and the illness. This was extremely valuable, since it allowed us to influence in some degree the environment to which the patient was to return.

The obvious limitations of this initial study can permit it to be considered only as an exploratory one. This paper is, accordingly, a preliminary report. We believe that the method has established value. It must be emphasized that group therapy is not considered to be a short-cut method, but, rather, that it is an additional therapeutic weapon in the treatment of schizophrenia. However, it can be used with insulin coma not only under optimum conditions, but also where time is at a premium. Psychotherapy is an integral part of insulin coma therapy and serves to consolidate the gains of physiological treatment.

SUMMARY

1. Our concept of the dynamics of schizophrenia is presented briefly as the basis for the psychotherapeutic method described.

2. Physiological and psychological factors of insulin coma treatment are considered.

3. Three types of therapeutic groups used in conjunction with, and subsequent to, insulin coma treatment are described: (*a*) the discussion group, (*b*) the picture-stimulus group, and (*c*) the follow-up contact group.

4. The conclusion is drawn that adequate treatment of schizophrenia must include psychotherapy and that certain types of group therapy are useful additions to the psychotherapeutic program.

TITRATION OF CENTRAL-NERVOUS-SYSTEM DEPRESSION

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AND
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DETROIT

IN THE organism receiving hypnotics the resulting depression of the central nervous system has commonly been divided into three stages, namely, sedation, hypnosis, and general anesthesia. The different stages are customarily ascertained by the signs and symptoms of a subject receiving the depressant. Sedation is recognized primarily as a prehypnotic stage of depression. It is evident that the effective doses, the dose range, and the degree of depression as estimated by such criteria are only approximate values. Therefore, an accurate method is desirable whereby the end-points for the three stages of depression may be easily detected and the depth of depression may be expressed in quantitative terms. The procedure to be described in this paper was designed to meet these requirements.

The method is based on the antagonism between a central-nervous-system depressant and a stimulant. The increase in quantity of the stimulant required to produce convulsions in animals is used as a measure of the degree of central depression. The results obtained with three central-nervous-system stimulants (pentylenetetrazol [metrazol*], picrotoxin, and strychnine) and five depressants (barbital sodium, phenobarbital sodium, pentobarbital sodium, trimethadione, and carbromal [bromodiethylacetylurea]) will be presented and explained.

EXPERIMENTAL INVESTIGATION

Rats of the same sex from the same stock weighing between 100 and 140 gm. were used in each experiment. The central-nervous-system depressant was given intraperitoneally to fed rats or orally to fasted rats. A half-hour later the convulsant was injected intramuscularly. The animals were then observed for 36 minutes for signs and symptoms. The jerking of the head, together with spasm of facial muscles, was considered as a minimal convulsive response. For each dose of the depressant, three groups of 10 rats each were given graded doses of the convulsant (20 to 80% of the convulsive level) for estimation of a stimulating dose which would produce convulsions in 50% of the animals. The CD_{50} value was interpolated graphically from the probit-logarithmic dose regression line (Miller and Tainter [1]).

1. Miller, L. C., and Tainter, M. L.: Estimation of the ED_{50} and Its Error by Means of Logarithmic-Probit Graph Paper, Proc. Soc. Exper. Biol. & Med. **57**:261, 1944.

Graphical Presentation of Data.—The CD_{50}'s and the corresponding doses of the depressant are plotted on the ordinate and on the abscissa, respectively. The following simple mass-action equation is utilized to fit the experimental data (Clark [2]; Gaddum [3]):

$$K_1C_1 = 1 + \frac{\alpha}{1-\alpha} \quad K_2C_2$$

Where

C_1 and C_2 = concentrations (doses) of a stimulant and a depressant, respectively;
α = per cent response (convulsions), and K_1 and K_2 are constants.

When the response is set at the 50% convulsive level, $\frac{\alpha}{1-\alpha} = 1$, the equation becomes

$$K_1C_1 = 1 + K_2C_2, \text{ or } C_1 = \frac{1}{K_1} + \frac{K_2}{K_1} C_2$$

A straight line is obtained in a C_1:C_2 plot. The intercept $\frac{1}{K_1}$ gives the CD_{50} value of a stimulant when the central nervous system is not under the influence of a depressant. The constant K_1 represents its central nervous system-stimulating potency. The slope, K_2/K_1 indicates the central nervous system-depressive action of an agent against a stimulant. In other words, the value K_2 is a measure of the central depressive potency.

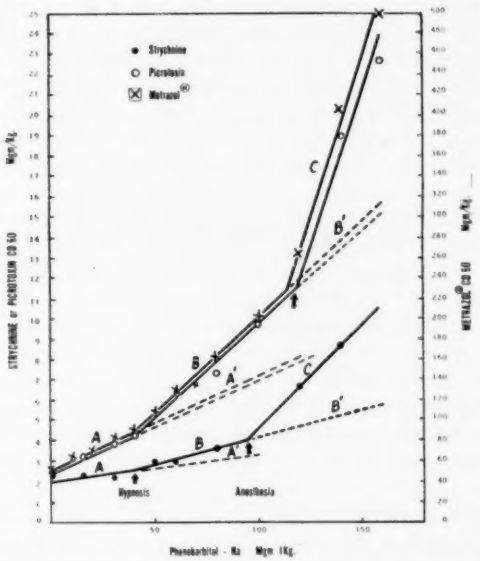

Chart 1.—Depressive effect on the central nervous system of phenobarbital sodium in rats, as determined by its anticonvulsant activity against strychnine, picrotoxin, and metrazol.®

The first point of inflection indicates a minimal hypnotic dose; the second point of inflection, a minimal anesthetic dose. The three solid lines with increasing dosage represent the stages of sedation (A), hypnosis (B) and general anesthesia (C).

RESULTS AND COMMENT

Our first attempt was to choose a central-nervous-system stimulant which may best be utilized experimentally for evaluating the activity of a central depressant.

2. Clark, A. J.: General Pharmacology, in Heffter, A.; Heubner, W., and others: Handbuch der experimentelle Pharmakologie 1937, Vol. 4, p. 185.

3. Gaddum, J. H.: The Antagonism of Drugs, Tr. Faraday Soc. **39**:323, 1943.

The data obtained in experiments with phenobarbital and the three convulsive agents (strychnine, picrotoxin, and metrazol*) are recorded in Table 1 and graphically presented in Chart 1. A salient feature shown in the graph is that each curve consists of two points of inflection at which a sudden change in slope appears. For practical considerations, the curve may be regarded as composed of three straight lines which intersect at points where hypnosis and general anesthesia occur. They represent, then, with increasing dosage the three stages of central-nervous-system depression: sedation (A), hypnosis (B), and general anesthesia (C). The value on the abscissa for the first (lower) intersect is a minimal hypnotic dose, and that for the second intersect is a threshold dose for anesthesia. The values between the intersects give the dose range for sedation, hypnosis, and anesthesia (between the anesthetic and the lethal dose). The corresponding CD_{50}'s on the ordinate over that for the untreated rats represent the anticonvulsant activities for sedative action, a joint sedative and hypnotic action at the hypnotic level, and a combined sedative, hypnotic, and anesthetic action during anesthesia. It is to be expected that the central depressive effect of a substance, as determined by the various central-nervous-system stimulants, should be the same quantitatively, provided their mode of action is similar. This is so indicated by the similarity in characteristics of the lines obtained with picrotoxin and metrazol.*

A further analysis of the data graphically and numerically by the mass-action equation is given in Section B of Table 1. The values are expressed both in milligrams and in equivalents. From the intercept the central-nervous-system-stimulating activity (K_1) was calculated. Strychnine and picrotoxin were found to be equally active, while metrazol* was about one-ninetieth as active as strychnine in causing convulsions. The sedative potency (K_2) of phenobarbital, computed from the slope of the first line, $(K_2/K_1)S$, is of the same magnitude against picrotoxin and against metrazol* (5.25 and 4.77, in equivalents of the convulsant per equivalent of phenobarbital sodium); the value against strychnine is less (2.04). The hypnotic threshold (H_1), 40 mg. per kilogram, is the same as determined with the three convulsants. At this dose, ataxia and signs of hypnosis are seen in some animals. The maximal depth of prehypnotic sedation, indicated by the symbol (S_1), is in this case at the level of minimal hypnosis; it is represented by the corresponding CD_{50} value on the ordinate—minus the CD_{50} of the untreated controls—as an anticonvulsant effect.

In computing the hypnotic potency, sedation was assumed to proceed linearly with dosage, as marked by the dotted line in the graph. The hypnotic component is then given by the difference in ordinates between the solid and the dotted line. This difference in value on the ordinate divided by the amount of a depressant above its minimal hypnotic level required to produce hypnosis gives the hypnotic effect per milligram of the drug. By the geometric principle for similar triangles, it may be shown that the amount of convulsant (CD_{50}) required to antagonize the hypnotic action of each unit increase of the depressant is a constant quantity. This may be taken as a measure of hypnotic potency. For example, as indicated by the graph for picrotoxin and phenobarbital, the difference on the ordinate between the solid line (B) and the dotted line (A') at 119 mg. of phenobarbital per kilogram of body weight is 11.5 — 7.8 mg. of picrotoxin per kilogram, and this divided by the difference between 119 mg. per kilogram and its minimal hypnotic dose (40 mg.

per kilogram), namely, a ratio of 3.7 : 79, or 0.047, is the hypnotic potency. The convulsant values so calculated, expressed both in milligrams per kilogram of convulsant per milligram per kilogram of depressant or in the equivalent amount of convulsant per equivalent of depressant, are given in Table 1 with the notation K_H. The ratio of the value for hypnotic potency to that for minimal hypnosis, K_H/S_1 is about the same (5.67, 5.97, and 5.21, in equivalents of the convulsant per equivalent of pheno-

TABLE 1.—*Effect of Phenobarbital on Strychnine-, Picrotoxin-, and Metrazol®-Induced Convulsions in Rats*

Phenobarbital Sodium Mg./Kg. (I. P.)	Strychnine Nitrate CD_{50} Mg./Kg. (I. M.)	Picrotoxin CD_{50} Mg./Kg. (I. M.)	Metrazol® CD_{50} Mg./Kg. (I. M.)
0	1.95	2.34	52.0
10	....	....	63.1
15	2.24	3.24	....
20	....	....	68.7
30	2.29	3.80	81.7
40	2.57	4.32	88.7
50	2.92	5.31	109.4
60	2.93	6.24	130.6
70	....	....	135.5
80	3.60	7.33	162.2
100	4.79	9.78	203.7
120	6.86	11.6	264.9
140	8.81	19.7	407.4
160	10.60	22.8	500.0

Notation*	Phenobarbital Sodium Mg./Kg.	Strychnine Nitrate Mg./Kg.†	Strychnine Nitrate Eq./Kg.†	Picrotoxin Mg./Kg.	Picrotoxin Eq./Kg.	Metrazol® Mg./Kg.	Metrazol® Eq./Kg.
		Analysis of Data by Mass-Action Equation					
$1/K_1$ (CD_{50})	..	1.95	0.005	2.40	0.004	52.0	0.377
K_1	..	204.1		250.0		2.66	
$(K_2/K_1)\,S$	..	0.016	0.010	0.048	0.021	0.975	1.79
K_2	..	2.04		5.25		4.77	
H_1	40	(for strychnine, picrotoxin and metrazol®)					
S_1	..	0.60	0.0015	1.96	0.003	39.0	0.282
K_H	..	0.013	0.009	0.047	0.020	0.80	1.47
K_H/S_1	..	5.67		5.97		5.21	
A	94,119,115	(strychnine, picrotoxin, metrazol®)					
H_2	..	0.75	0.002	3.70	0.006	72.0	0.521
K_A	..	0.075	0.048	0.219	0.093	4.13	7.60
K_A/H_2	..	25.3		15.2		14.6	

* $1/K_1$ indicates intercept; K_1, convulsive potency; $(K_2/K_1)\,S$, slope of first line; K_2, sedative potency in anticonvulsant effect; H_1, minimal hypnotic dose; S_1, depth of prehypnotic sedation; K_H, hypnotic potency in anticonvulsant effect; A, minimal anesthetic dose; H_2, maximal preanesthetic hypnosis; K_A, anesthetic potency.

† Milligrams per kilogram of convulsant per milligrams per kilogram of depressant, or equivalent amount of convulsant per equivalent amount of depressant.

barbital-sodium) as that obtained with strychnine, picrotoxin, and metrazol® convulsions.

The minimal anesthetic dose (A) of phenobarbital was found to be less against strychnine-induced convulsions than against pictrotoxin- or metrazol®-induced convulsions (94, 119, and 115 mg. per kilogram, respectively). By assuming that both sedation and hypnosis continue to increase linearly with the dosage during anesthesia, we calculated graphically the values for maximal hypnosis or minimal anesthesia (H_2), and for anesthetic potency (K_A) as in the case of hypnotic potency. It should be emphasized here that the sedative, hypnotic, and anesthetic potencies mentioned in this paper are given by the slopes of the dose-response lines. The

term "potency" thus differs from that ordinarily implied in that it is not based on a minimal effective dose level. The ratios of the anesthetic potency value to the minimal anesthesia value, K_A/H_2, were computed and found to be 15.2 and 14.6, respectively, against picrotoxin and metrazol® convulsions and 25.3 against strychnine convulsions. The larger value obtained with strychnine is due primarily to the smaller equivalent quantity of strychnine required than that of picrotoxin or metrazol® to produce convulsions in rats under hypnosis. The increased reflex excitability produced by strychnine, and consequently the effect of external stimuli, may partially account for its greater convulsive effect.

Because of the influence of external stimuli, strychnine is not preferred for the determination of the central-nervous-system depressive activity of drugs. As between picrotoxin and metrazol,® the latter is readily soluble in water, and in equivalent convulsive doses its onset is more rapid and the duration of its convulsive effect shorter. Metrazol® was thus chosen for use in our comparison of the central depressive potencies of the various agents.

Activities of Some Central-Nervous-System Depressants.—The results obtained with metrazol® and five depressants (barbital, phenobarbital, pentobarbital, trimethadione, and carbromal) are given in Table 2 and in Charts 2 and 3. In the order of decreasing sedative potency (K_2), as well as minimal hypnotic doses (H_1), the depressants occur as follows: pentobarbital, carbromal, phenobarbital, barbital, and trimethadione. The total prehypnotic sedation, as shown by the anti-metrazol® effect (S_1), is, however, greater for an agent which is low in sedative potency.

With the exception of carbromal, these drugs have hypnotic and anesthetic potencies (K_H and K_A) of the same order of activity as that for sedation. Their minimal hypnotic and anesthetic doses (H_1 and A in Table 2), given in milligrams per kilogram of body weight, are as follows: pentobarbital, 15.0 and 31.5; phenobarbital, 40 and 115; barbital, 168 and 278, and trimethadione, 700 and 1,200. It is of interest to note that, whereas the minimal hypnotic dose of phenobarbital is one-fourth that of barbital, the two are equally potent in their hypnotic and anesthetic action, as indicated by the slopes of the respective lines. The maximal *depth* of preanesthetic hypnosis (H_2) is, as in the case of maximal prehypnotic sedation, greater for a weaker hypnotic agent; the difference, however, between the barbiturates is slight. The ratio of the value for hypnotic potency to that for total prehypnotic sedation (K_H/S_1), and the ratio of the value for anesthetic potency to that for maximal depth of preanesthetic hypnosis (K_A/H_2) indicate the usefulness of these compounds as sedative, hypnotic, or anesthetic agents. Pentobarbital (with the highest ratio) should be the best agent for producing hypnosis and general anesthesia, but poor for sedation. The reverse should be true for trimethadione (with the lowest ratio). Barbital and phenobarbital are expected to be fairly effective hypnotic and anesthetic agents.

The hypnotic range (A-H) and the anesthetic range of doses (LD_{50}-A) of the various depressants, given in Table 2, are, as is to be expected, in an inverse relationship to their potencies (K_H, K_A). However, when the margin of safety of a depressant is taken with reference to its minimal effective dose, as indicated by the ratio of the anesthetic to the hypnotic dose (A/H) or the ratio of LD_{50} to the anesthetic dose (LD_{50}/A), phenobarbital (a ratio of 2.9) and pentobarbital (a ratio of 2.8) have the highest margins of safety, respectively, as hypnotic and as anesthetic

TABLE 2.—*Effect of Central-Nervous-System Depressants on Metrazol®-Induced Convulsions in Rats*

Mg./Kg. I. P. Barbital	Mg./Kg. CD_{50} I. M. Metrazol®	Mg./Kg. I. P. Phenobarbital	Mg./Kg. CD_{50} I. M. Metrazol®	Mg./Kg. I. P. Pentobarbital	Mg./Kg. CD_{50} I. M. Metrazol®	Mg./Kg. I. P. Trimethadione	Mg./Kg. CD_{50} I. M. Metrazol®	Mg./Kg. Oral Carbromal	Mg./Kg. CD_{50} I. M. Metrazol®
0	57.0	0	52.0	0	50.4	0	53.7	0	50.7
20	82.2	10	63.1	5	63.8	100	57.5	20	77.6
40	91.0	20	68.7	10	72.8	250	85.1	40	105.3
60	103.5	30	81.7	15	84.1	400	100.3	60	146.6
80	118.3	40	88.1	20	116.9	550	131.8	80	169.6
120	150.6	50	109.4	25	141.9	700	144.5	120	241.6
160	176.5	60	130.6	30	163.3	850	223.9	160	277.6
200	252.6	70	135.5	35	254.1	1,000	295.1	240	319.9
240	290.6	80	162.2	40	346.7	1,200	371.5	400	389.0
280	384.9	100	203.7	45	457.1	1,400	562.3	640	494.3
320	582.4	120	264.9			1,600	783.4	1,000	699.5
360	851.1	140	407.4						
		160	500.0						

Analysis of Data by Mass-Action Equation

Notation*	Barbital Mg./Kg.	Metrazol® Mg./Kg.	Metrazol® Eq.	Phenobarbital Mg./Kg.	Metrazol® Mg./Kg.	Metrazol® Eq.	Pentobarbital Mg./Kg.	Metrazol® Mg./Kg.	Metrazol® Eq.	Trimethadione Mg./Kg.	Metrazol® Mg./Kg.	Metrazol® Eq.	Carbromal Mg./Kg.	Metrazol® Mg./Kg.	Metrazol® Eq.
$1/K_1$	..	59.0	0.427	..	52.0	0.377	..	53.0	0.384	..	54.0	0.391	..	52.0	0.377
K_1	..	2.34		..	2.66		..	2.61		..	2.59		..	2.66	
$(K_2/K_1)\,S$	..	0.760	1.13	..	0.975	1.79	..	2.06	3.79	..	0.132	0.14	..	1.35	2.32
K_2	..	2.65		..	4.77		..	9.88		..	0.35		..	6.16	
H_1	168 (0.815 eq.)	.....	.....	40 (0.157 eq.)	.....	.....	15 (0.059 eq.)	.....	.....	700 (4.895 eq.)	.....	.....	40 (0.169 eq.)	.....	.....
S_1	..	128	0.93	..	39	0.28	..	31	0.23	..	92	0.67	..	50	0.36
K_{II}	..	0.84	1.25	..	0.80	1.47	..	3.60	6.62	..	0.38	0.39	..	.....	.....
K_{II}/S_1	..	1.35		..	5.22		..	29.4		..	0.52		..	.....	.....
A	278 (1.35 eq.)	.....	.....	115 (0.45 eq.)	.....	.....	31.5 (0.12 eq.)	.....	.....	1,220 (8.54 eq.)	.....	.....	..	.....	.....
H_2	..	91	0.66	..	72	0.52	..	60	0.44	..	188	1.36	..	.....	.....
K_4	..	3.80	5.66	..	3.40	6.26	..	14.71	26.33	..	0.53	0.55	..	.....	.....
K_4/H_2	..	8.59		..	12.01		..	60.53		..	0.40		..	.....	.....
$LD_{50} \pm$ S. D.†	360 ± 48	.....	.....	183 ± 22	.....	.....	90 ± 13	.....	.....	2,000	.....	.....	..	.....	.....
A-H_1	110	.....	.....	75	.....	.....	16.5	.....	.....	520	.....	.....	..	.....	.....
A/H_1	1.7	.....	.....	2.9	.....	.....	2.1	.....	.....	1.7	.....	.....	..	.....	.....
LD_{50}-A	82	.....	.....	68	.....	.....	58	.....	.....	780	.....	.....	..	.....	.....
LD_{50}/A	1.3	.....	.....	1.6	.....	.....	2.8	.....	.....	1.6	.....	.....	..	.....	.....

* For interpretation of symbols, see Table 1.
† Four groups of 10 rats each were given a graded lethal dose of a depressant; the LD_{50} and standard errors were computed graphically from the probit-logarithmic regression line.

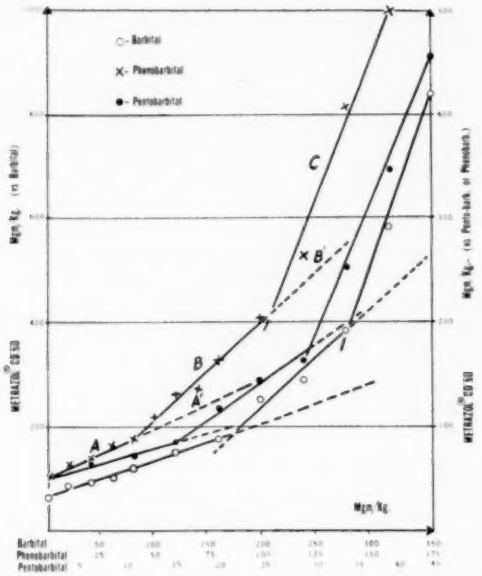

Chart 2.—Depressive effects on the central nervous system of barbital sodium, phenobarbital sodium, and pentobarbital sodium in rats, as determined by their anticonvulsant activity against metrazol.®

The lines and inflection points indicate the dose range for sedation, hypnosis, and general anesthesia, and the depressive potencies of the three barbiturates on the central nervous system.

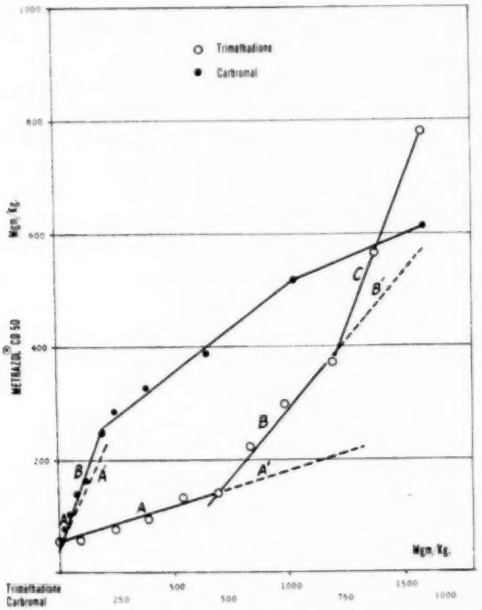

Chart 3.—Depressive effects on the central nervous system of trimethadione and carbromal in rats, as measured by their anticonvulsant activity against metrazol.®

Trimethadione shows the three stages of central-nervous-system depression, as do the barbiturates. The first inflection on the lines for carbromal is very slight, indicating a very weak hypnotic action; there is no evidence of general anesthesia at higher doses.

agents. Apparently, the range of hypnotic doses or that of anesthetic doses of a depressant is not based entirely upon its minimal effective dose or its potency.

As evidenced by a slight difference in slopes of the lines for sedation and hypnosis for carbromal in Chart 3, this drug is a poor hypnotic agent. It was found that rats which received 1 gm. of carbromal per kilogram of body weight (25 times the hypnotic threshold of the drug) were not in deep hypnosis. Complete anesthesia could be induced only with a lethal dose of 2 gm. of carbromal. The results indicate clearly that sedation is not merely a low degree of hypnosis but is a different affection in central-nervous-system depression. From the standpoint of its anticonvulsant activity and its poor hypnotic action, carbromal is therefore a good sedative agent. The decrease in slope of the carbromal curve with increasing dosage may partially be due to a slow absorption from the gastrointestinal tract.

Trimethadione was included in our study for the reason that, on the basis of its anticonvulsant action against metrazol® and its effectiveness in the control of petit mal epilepsy, the anti-metrazol® test has been extensively employed for the screening of potential antiepileptic drugs. In light of the evidence here presented, the anti-metrazol® activity of a substance below hypnotic level is simply a measure of its sedative action, a property common to most central-nervous-system depressants. Sedation, evidently, is a vague term implying suppression of central-nervous-system activity of various centers. A compound like trimethadione apparently suppresses also the excitability of an epileptic focus, while most of the barbiturates do not possess such an action below hypnotic levels. The revelation of the site of action of the various sedative agents will add greatly to the discovery of new drugs for the management of disorders of the central nervous system.

SUMMARY

A method for the quantitative titration of depression of the central nervous system, based upon the antagonism between a central depressant and a convulsant, is described. By plotting the CD_{50}'s of a stimulant against the corresponding doses of the depressant, three straight lines are constructed for sedation, hypnosis, and general anesthesia, respectively. The slopes and the intersects of the lines represent the sedative, hypnotic, and anesthetic potencies of a drug and its minimal hypnotic and anesthetic doses, respectively. The depth of the three stages of depression is indicated by its anticonvulsant effect.

The relation of dose to the depressive effect of phenobarbital was determined against convulsions induced by strychnine, picrotoxin, and pentylenetetrazol (metrazol®). No difference was found in the quantitation of central-nervous-system depression with the three convulsants.

Metrazol® was used to study the depressive effect on the central nervous system of pentobarbital, phenobarbital, barbital, trimethadione, and carbromal (bromodiethylacetylurea). The results indicate the usefulness of these agents for sedation, hypnosis, or general anesthesia. The three barbiturates are more effective agents for producing hypnosis and general anesthesia, whereas trimethadione and carbromal are better drugs for sedation.

BLOOD KETONE CONCENTRATION IN PATIENTS WITH MENTAL AND EMOTIONAL DISORDERS

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ABNORMALITIES in the production of ketone bodies have been studied in patients with mental disease for over 60 years. Ketonuria has been found by a number of investigators [1]; more important are observations showing that the rate of formation of ketone bodies is abnormally high in schizophrenia.[1d,f] The blood ketone-body concentration has not been investigated so thoroughly. Freudenberg and Fine [2] found that blood ketones were increased in two of five schizophrenic patients studied; Greving [3] reported abnormal increases during exercise. In a more recent study, Hinkle and associates [4] reported increases in blood ketones in normal

Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

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1. (*a*) Laignel-Lavastine, M., and Cornelius, R.: Le titrage des acides organiques de l'urine par la méthode de Van Slyke et Palmer chez les anxieux et les déprivés, Compt. rend. Soc. biol. **89**:160, 1923; (*b*) De l'alcalinite ionique des urines et du sang chez les anxieux, J. méd. franç. **19**:261, 1930. (*c*) Shattock, F. M.: Somatic Manifestations of Schizophrenia: Clinical Study of Their Significance, J. Ment. Sc. **96**:32, 1950. (*d*) Thompson, J. W., and Aste-Salazar, J. H.: Ketonemia in Cases of Mental Disorders, Arch. Neurol. & Psychiat. **41**:375, 1939. (*e*) Lingjaerde, O.: Leberuntersuchungen bei Geisteskranken unter besonderer Berücksichtigung des Verhältnisses von Krankheitsverlauf, Leberfunktion und Nahrungszufuhr bei Schizophrenen, Acta psychiat. et neurol., Supp. 5, 1934. (*f*) Northcote, M. L. M.: Somatic Changes in the Psychoses: A Comprehensive Investigation of the Bodily Functions of 30 Psychotic Patients by Means of Clinical, Pathological, Biochemical, Pharmacological and Radiological Methods, J. Ment. Sc. **78**:263, 1932. (*g*) Gamble, F. M.: Some Laboratory Findings in the Routine Investigations of Acute Admissions, ibid. **76**:292, 1930. (*h*) Targowla, R.: L'azotémie et l'acidose dans la confusion mentale, Presse méd. **30**:225, 1922. (*i*) Targowla, R., and Badonnel, M.: Insuffisance hépato-rénale et altérations sanguines dans la mélancolie, Ann. med.-psychol., s. 11 **2**:346, 1921. (*j*) Rivano, F.: Sulla acetonuria negli alienati, Ann. freniat., Torino **1**:105, 1888. (*k*) Morault, Y.: L'acidose chez les aliénés, Thesis, Paris, 1921.

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3. Greving, H.: Pathophysiologische Beiträge zur Kenntnis körperlicher Vorgänge bei endogenen Psychosen, besonders bei der Schizophrenie, Arch. Psychiat. **112**:613, 1941.

4. Hinkle, L. E., Jr.; Conger, G. B., and Wolf, S.: Studies on Diabetes Mellitus: The Relation of Stressful Life Situations to the Concentration of Ketone Bodies in the Blood of Diabetic and Non-Diabetic Humans, J. Clin. Invest. **29**:754, 1950.

and diabetic subjects after mental stress, while Sargent and Consolazio [5] observed ketonuria in normal subjects in conditions of stress.

In view of the paucity of available data, it was decided to study the blood ketone-body concentration in a group of patients in a mental hospital.

MATERIAL AND METHODS

Measurements were made on blood obtained from 24 normal subjects who were members of the hospital staff and on 98 patients with various types of mental disorders (Chart 1). All measurements were made on venous blood drawn before breakfast after a 12-hour fast; in half the cases this was on the second or third day after the patient's admission to the hospital. All patients had adequate diets after entering the hospital. Forty-nine of the patients had been in the hospital for at least a month before the test was made; none had malnutrition.

The method used was a modification of that reported by Behre [6] and Greenberg and Lester.[7] A protein-free filtrate was prepared in the usual manner by adding zinc sulfate and sodium hydroxide to 2 ml. of blood and then adding water to make a total volume of 25 ml. The mixture was filtered, and 10 ml. of the filtrate was placed in a 50-ml. round-bottom flask, to which was added 3 drops of 20 N sulfuric acid and 1.2 ml. of a 0.46% solution of potassium dichromate

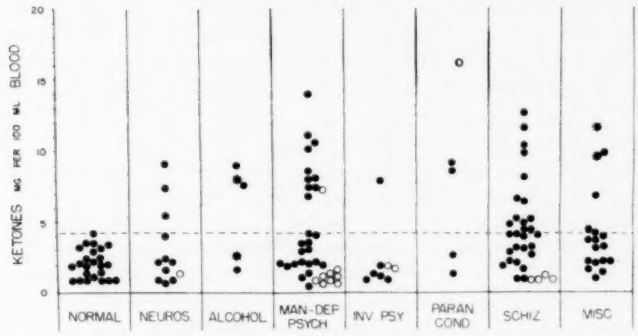

Chart 1.—Blood ketone concentrations in normal subjects and in patients. Open circles indicate values obtained after treatment; crenellated dots, values for patients with hepatic disease.

in 15.6 N sulfuric acid. The mixture was distilled through a Stotz condenser at a rate such that 8 ml. of distillate was obtained in 15 to 20 minutes, most of it in the last 5 minutes. The distillate was received in a calibrated test tube containing 4 ml. of a 2% solution of sodium bisulfite; 2 ml. of the contents of this tube were placed in another calibrated test tube, to which were added 0.1 ml. of salicylaldehyde and 1.5 ml. of a saturated solution of potassium hydroxide, the latter being blown in to secure immediate mixing. Twenty minutes later, a 75% solution of ethyl alcohol was added to make the volume up to 5 ml. The precipitate formed at this point was dissolved by vigorous stirring, and then alcohol solution was added to make the volume 10 ml.; this mixture was centrifuged if cloudy. The clear solution was placed in a Coleman spectrophotometer set at 540 A., and the reading was compared with a standard curve. The range of values obtained for the normal group in this study was somewhat higher than has

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6. Behre, J. A.: A Modified Salicylaldehyde Method for the Determination of Acetone Bodies in Blood and Urine, J. Biol. Chem. **136**:25, 1940.

7. Greenberg, L. A., and Lester, D.: A Micromethod for the Determination of Acetone and Ketone Bodies, J. Biol. Chem. **154**:177, 1944.

been reported in previous studies, in which a variety of methods were used.[8] The discrepancy is not significant, however, as ketone levels as high as 5 mg. per 100 ml. have frequently been found in an unselected normal population.[9]

OBSERVATIONS

The blood ketone-body concentration in the normal subjects ranged from 0.8 to 4.2 mg. per 100 ml. of blood. The patients as a whole showed values ranging from 0.4 to 16.2 mg. per 100 ml. of blood; 37 of the 98 patients, that is, 38% showed values that exceeded 4.2 mg. per 10 ml. (Chart 1). The patients with manic-depressive, involutional, paranoid, and schizophrenic psychoses showed an elevation in 26 of 64 instances, or 40% (Chart 1). Only three neurotic patients showed elevated values; they were considered by the clinical staff to be instances of reactive depressions. All patients in the manic-depressive group who had elevated values had been ill for less than one year; those ill for a longer time revealed values within the

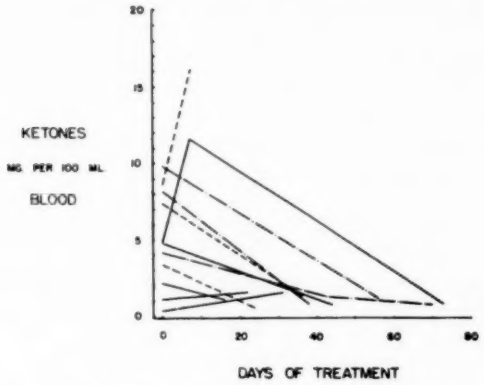

Chart 2.—Changes in blood ketone concentrations during the course of treatment. Solid lines indicate values obtained after electroshock therapy; lines of dashes and dots, values after insulin therapy, and the line of dashes, values after psychotherapy.

normal range. No correlation between blood ketone level and duration of disease can be made with respect to any of the other diagnostic categories.

While the study was in progress, 11 patients for whom admission values had been obtained were considered to show improvement after electroshock, insulin coma, or psychotherapy; 6 of these patients had elevated values on admission (Chart 2). In two patients studied in the first week of treatment a further rise occurred. Fasting blood ketone values were obtained in all patients after the end of treatment, usually on the morning of discharge from the hospital. Three patients in whom normal values were found on admission showed no change with treatment.

8. (*a*) Crandall, L. A., Jr.: A Comparison of Ketosis in Man and Dog, J. Biol. Chem. **138**:123, 1941. (*b*) Hubbard, R. S.: Determination of the Acetone Bodies in Blood, ibid. **49**:375, 1921. (*c*) Klein, D.: Determinations of Pyruvic Acid in Blood in the Presence of Acetoacetic Acid, ibid. **137**:311, 1941. (*d*) Somogyi, M.: Effect of Insulin upon the Production of Ketone Bodies, ibid. **141**:219, 1941.

9. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, Ed. 12, Philadelphia, The Blakiston Company, 1947.

Seven of the other eight patients showed decreases; those with abnormally high initial levels had normal values at the end of treatment, with one exception. The single patient with an aberrantly high value of 16.2 mg. per 100 ml. of blood at the time of discharge, although characterized as cured by the clinical staff, was readmitted to the hospital a few months later; she was a highly intelligent woman with a paranoid condition, who was given psychotherapy alone; after a short period of this treatment her comments were regarded by the psychiatrist as indicative of complete remission. Treatment in all cases was regulated by the clinical staff, who were unaware of the data presented here; it is of interest that the patients in whom normal initial values were found were considered improved after 16 to 31 days of treatment, whereas, with one exception, patients with high values were found by the clinical staff to require from 38 to 73 days of treatment. A pronounced fall in blood ketone level was not necessarily associated with lasting improvement.

COMMENT

Of the psychotic subjects, 40% had levels of blood ketone bodies that exceeded the upper limit for the normal group. Ketonemia is an evidence of increased catabolism of fat, a phenomenon that may have a number of causes, such as decreased reserves of hepatic glycogen,[10] severe exercise,[11] prolonged fasting,[8a] and the administration of epinephrine,[12] hormones of the anterior lobe of the pituitary or adrenocortical hormone.[13]

The conditions of the study minimized the possibility that dietary factors alone produced elevated values. However, it is impossible to state precisely what mechanisms might be involved in the production of ketonemia in psychotic patients. Moreover, no explanation can be offered for the occurrence of an elevated ketone level in manic-depressive patients who had been sick for less than one year, as contrasted with the normal values in more chronic patients.

The fall in blood ketone levels after improvement with therapy in the few patients so studied indicates that a decreased rate of fat catabolism accompanies remission in these patients; this finding is consistent with a decrease in output of hormones of the anterior lobe of the pituitary or the adrenal cortex.

SUMMARY

The blood ketone-body level was elevated in 40% of patients with manic-depressive, involutional, paranoid, or schizophrenic psychoses. It was also found to be elevated in several patients with severe neurosis and in alcoholic patients. In the case of manic-depressive psychosis elevated levels were found only in patients who had been ill for less than a year. The blood ketone level fell with improvement after therapy.

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13. Bennett, L. L.; Slesser, A., and Thorn, G. W.: Effect of Compound E on Blood Ketone Bodies, J. Clin. Endocrinol. **9**:675, 1949. Bennett, L. L.; Kreiss, R. E.; Li, C. H., and Evans, H. M.: Production of Ketosis by the Growth and Adreno-Corticotrophic Hormones, Am. J. Physiol. **152**:210, 1948.

JOINT EFFECT OF SOME CENTRAL-NERVOUS-SYSTEM DEPRESSANTS

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IN A PREVIOUS paper (Chen and Portman [1]) a method was described for the quantitative titration of central-nervous-system depression. It is based upon the anticonvulsant action of a depressant, whereby the sedative, hypnotic, and anesthetic potency may be expressed in terms of the amount of a convulsant required to antagonize the depression. Sedation, hypnosis, and general anesthesia, expressed in terms of anticonvulsant effect, and the dose of a depressant were shown to follow the simple equation of mass action in three linear relationships. The slopes of the lines indicate the potency of an agent for the three stages of depression. The intersects give the minimal hypnotic and minimal anesthetic doses. In this paper there will be presented data on the joint central depressive effect of barbital and pentobarbital and that of pentobarbital and carbromal (bromodiethylacetylurea), as determined by their anticonvulsant activity. The two barbiturates were found to be additive, whereas pentobarbital and carbromal were synergistic, in their anticonvulsant effects.

MATERIAL AND METHODS

Female Sprague-Dawley rats, weighing between 100 and 120 gm. were used. A solution of barbital sodium and pentobarbital sodium and a suspension of carbromal with pentobarbital in 7% acacia were given by intraperitoneal and oral administration, respectively. Half an hour later pentylenetetrazole U. S. P. (metrazol®) solution was injected intramuscularly. Three groups of 10 or 20 rats each receiving a dose of the depressant and three graded doses of metrazol® were employed for the determination of a CD_{50} dose. The doses of metrazol® were so adjusted as to produce convulsions in 20 to 80% of the animals. The CD_{50} value was interpreted from the probit-logarithmic dose regression line (Miller and Tainter [2]).

The joint effect of the depressants was investigated in two ways: 1. By their sedative action. The amount of a depressant which produces a maximal prehypnotic sedation (a minimal hypnotic dose) was chosen as an equivalent sedative dose. The joint anti-metrazol® effects of the two depressants at an equivalent dose level in various proportions of one to the other were measured (Loewe and Muisechnek.[3]) 2. By their sedative and hypnotic action. In this the anti-metrazol® activities of the individual depressants and their combination at sedative and hypnotic levels were

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2. Miller, L. C., and Tainter, M. L.: Estimation of the ED_{50} and Its Error by Means of Logarithmic-Probit Graph Paper, Proc. Soc. Exper. Biol. & Med. **57**:261, 1944.

3. Loewe, S., and Muisechnek, F.: Über Kombinationswirkungen: I. Hilfsmittel Fragestellung, Arch. exper. Path. u. Pharmakol. **114**:313, 1926.

TABLE 1.—*Joint Anti-Metrazol® Effects of Barbital plus Pentobarbital and Pentobarbital plus Carbromal in Rats*

(A) Barbital + Pentobarbital (I.P.)			(B) Pentobarbital + Carbromal (Oral)		
Barbital Mg./Kg.	Pentobarbital Mg./Kg.	Metrazol (I.M.)* CD_{50} Mg./Kg.	Pentobarbital Mg./Kg.	Carbromal Mg./Kg.	Metrazol (I.M.)* CD_{50} Mg./Kg. ± S.E.
0	15.00	96.3	15.00	0	100 ± 4.1
40	11.25	120.3	11.25	10.0	112 ± 1.5
80	7.50	151.7	7.50	20.0	128 ± 3.8
120	3.75	183.3	3.75	30.0	130 ± 2.4
160	0	197.7	0	40.0	120 ± 3.8

* The CD_{50} was determined with three doses of metrazol® in three groups of 20 rats each.

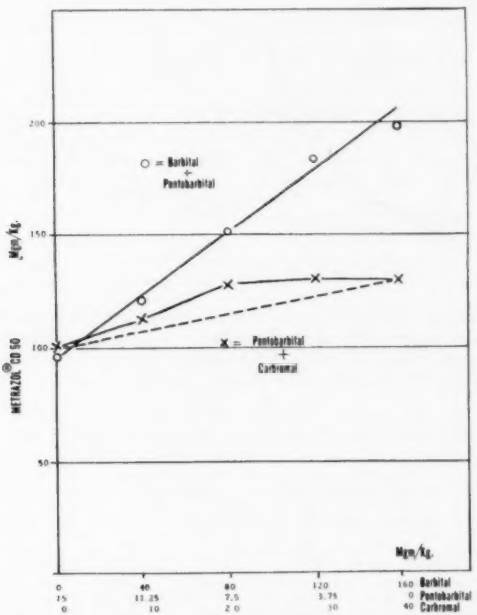

Chart 1.—Joint anti-metrazol® effects of pentobarbital and barbital and of pentobarbital and carbromal at equivalent sedative doses in rats.

The straight line for barbital and pentobarbital signifies an additive joint effect, whereas the curve for pentobarbital and carbromal indicates a synergistic action.

determined in the same experiment. From the experimental curves for each depressant, the anti-metrazol® effect of the combination was calculated for an additive action; this was compared with the experimental value for the combination.

RESULTS AND COMMENT

In Table 1 and Chart 1 are presented the data obtained from experiments with equivalent sedative doses of the combination of barbital and pentobarbital and of the combination of pentobarbital and carbromal. The linear relationship between the anticonvulsant activity (CD_{50} doses of metrazol®) and the equivalent doses of

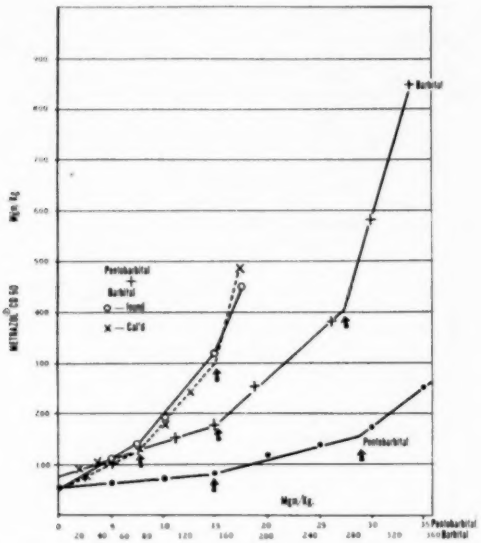

Chart 2.—Individual and joint anti-metrazol* effects of barbital and pentobarbital in rats.

The inflection points indicated by arrows correspond to a minimal hypnotic level at low dosage and a minimal anesthetic level at higher dosage. The slopes of the lines represent the sedative, hypnotic, and anesthetic potencies of the depressant.

TABLE 2.—*Individual and Joint Anti-Metrazol* Effects of Pentobarbital and Barbital in Rats*

Pentobarbital (I.P.) Mg./Kg.	Metrazol® (I.M.) CD50 Mg./Kg.	Barbital (I.P.) Mg./Kg.	Metrazol® (I.M.) CD50 Mg./Kg.	Pentobarbital + Barbital (I.P.)		Metrazol® (I.M.) CD50 Mg./Kg.	
				Mg./Kg.	Mg./Kg.	Found	Calc.*
0	50.4	0	57.0	0	0	52.5	.....
5	63.8	20	82.2	2.5	26.7	78.5	77.4
10	72.8	40	91.0	5.0	53.3	110.9	102.9
15 †	84.1	60	103.5	7.5 †	80.0 †	142.9	128.3
20	116.9	80	118.3	10.0	106.7	190.5	185.2
25	141.9	120	150.6	12.5	133.4	238.8	242.1
30 ‡	163.3	160 †	176.5	15.0 ‡	160.0 ‡	319.9	299.2
35	254.1	200	252.6	17.5	186.7	451.9	494.0
40	346.7	240	290.6				
45	457.1	280 ‡	384.9				
		320	582.4				
		360	851.1				

$K_S = 2.06$ $K_S = 0.76$ (sedative potency, obtained from Chart 2)
$K_H = 3.60$ $K_H = 0.84$ (hypnotic potency, obtained from Chart 2)
$K_A = 14.71$ $K_A = 3.80$ (anesthetic potency, obtained from Chart 2)

* Sum of individual effects.
† Minimal hypnotic dose.
‡ Minimal anesthetic dose.

barbital and pentobarbital in various proportions signifies an additive joint action. The curve for the combination of pentobarbital and carbromal, on the other hand, indicates a synergistic joint action; its curvature shows the intensity of synergism.

The results given in Tables 2 and 3 were obtained by using a combination of the two central-nervous-system depressants in fractions and in multiples of their minimal hypnotic doses. It is seen in Chart 2 that the minimal hypnotic and anesthetic doses for barbital and pentobarbital are 160 and 296 mg. and 15 and 29 mg. respectively, per kilogram of body weight (by the intersects of the lines). The minimal hypnotic and anesthetic values for the combination are the sum of half of their individual doses. The anti-metrazol® effect of the combination is equal to that calculated for an additive joint action (dotted line). As an example, the calculation for the

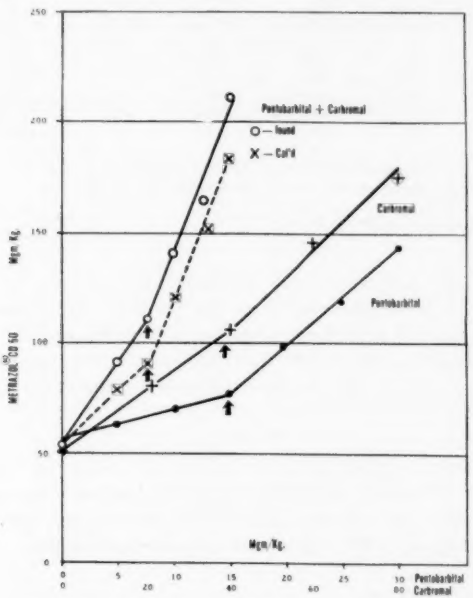

Chart 3.—Individual and joint anti-metrazol® effects of pentobarbital and carbromal in rats. The point of inflection marked by an arrow indicates the level of minimal hypnosis. The lines below and above the inflection represent, respectively, the sedative and hypnotic stages.

anti-metrazol® effect of a combination of 15 mg. of pentobarbital and 160 mg. of barbital, per kilogram of body weight, is performed as follows: At first, as shown by the point on the curve for the combination at these doses in Chart 2, it is a maximal hypnotic level before general anesthesia occurs. The central depressive effect of this combination thus consists of the sedative and hypnotic effects of the two components. The effect of pentobarbital is equal to 15 × 2.06 (sedative potency, Table 2) plus 7.5 × 3.60 (hypnotic potency, Table 2), since hypnosis occurs at 7.5 mg. of pentobarbital per kilogram of body weight in the combination, a total of 57.90 mg. per kilogram of metrazol® antagonized. Likewise, the effect of barbital is 160 × 0.76 (sedative potency) plus 80 × 0.84 (hypnotic potency), a total of

188.8 mg. per kilogram of metrazol® antagonized. The sum of the two (57.90 + 188.80) plus the CD_{50} for rats without treatment (52.5 mg. per kilogram of metrazol®) is 299.2 mg. per kilogram (Table 2). The difference between the experimental and the calculated values for all the determinations is within ± 10%.

Chart 3 is a graphic presentation of the joint anti-metrazol® effect of pentobarbital and carbromal. The minimal hypnotic dose of the combination is shown to be the sum of one-half the individual doses. The experimental anti-metrazol® values, on the other hand, are uniformly higher than those calculated for an additive action

TABLE 3.—*Individual and Joint Anti-Metrazol® Effects of Pentobarbital and Carbromal in Rats*

Pentobarbital (Oral) Mg./Kg.	Metrazol® (I.M.) CD_{50} Mg./Kg.	Carbromal (Oral) Mg./Kg.	Metrazol® (I.M.) CD_{50} Mg./Kg.	Pentobarbital + Carbromal (Oral) Mg./Kg.	Pentobarbital + Carbromal (Oral) Mg./Kg.	Metrazol® (I.M.) CD_{50} Mg./Kg. Found	Metrazol® (I.M.) CD_{50} Mg./Kg. Calc.*
0	50.1	0	50.7	0	0	54.0	.....
5	64.2	20	77.6	5	13.3	91.2	78.4
10	70.8	40 †	104.7	7.5 †	20.0 †	110.9	90.6
15 †	76.7	60	146.6	10.0	26.7	139.6	121.6
20	97.1	80	176.2	12.5	33.3	165.2	152.5
25	118.9	120	254.1	15.0	40.0	211.8	183.5
30	142.9						

$K_S = 1.4$ $K_S = 1.3$ (sedative potency, obtained from Chart 3)
$K_H = 2.9$ $K_H = 0.43$ (hypnotic potency, obtained from Chart 3)

* Calculated for additive joint effect.
† Minimal hypnotic dose.

(dotted line), a greater difference being for those due to a sedative effect (14 to 18%, Table 3). This is in agreement with the previous results obtained by the equivalent sedative doses of pentobarbital and carbromal. Apparently, pentobarbital and carbromal synergize in their central-nervous-system depression primarily in sedation, an effect which is included in their anti-metrazol® action at hypnotic levels.

SUMMARY

A procedure is presented for the study of the joint effect of central-nervous-system depressants. It is based upon their anticonvulsant activity against metrazol.® Barbital and pentobarbital were shown to be additive, and pentobarbital and carbromal were synergistic, in their combined anticonvulsant effect.

ROLE OF GELATINOUS SUBSTANCE OF SPINAL CORD IN CONDUCTION OF PAIN

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THE PATHS of the dorsal root fibers into Lissauer's zone and the dorsal funiculus of the spinal cord are well established. The manner of the termination of these fibers within the gray matter of the spinal cord and the pattern of the connecting neurons are not so well understood. This is particularly true of the human spinal cord.

Although this problem has been studied by Ramón y Cajal,[1] Ranson,[2] and others, there are still wide gaps in our knowledge of these connections. The majority of the studies on this subject have been based on the lower vertebrate forms, such as the chick and cat, with few observations on the higher mammals and man. Since the early literature on this subject has been reviewed by Barker[3]; Ranson[4]; Massazza[5]; Bok,[6] and Ariëns Kappers, Huber, and Crosby,[7] only the more recent investigations will be discussed.

MATERIALS AND METHODS

The usual neurological preparations show little of the structural detail or the synaptic connections within the posterior gray columns of the spinal cord. Ramón y Cajal, C. Judson Herrick, and Lorente de Nó have demonstrated many times that the Golgi method is one of the most instructive approaches to a problem of this type. The present study is based largely on Golgi

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This investigation was supported in part by a grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

1. Ramón y Cajal, S.: Histologie du système nerveux de l'homme et des vertébrés, translated from the Spanish by L. Azoulay, Paris, A. Maloine, 1909, Vol. 1.

2. Ranson, S. W.: Course Within the Spinal Cord of the Non-Medullated Fibers of the Dorsal Roots: A Study of Lissauer's Tract in the Cat, J. Comp. Neurol. **23**:259-281, 1913.

3. Barker, L. F.: The Nervous System and Its Constituent Neurones, Designed for the Use of Practitioners of Medicine and of Students of Medicine and Psychology, New York, D. Appleton & Co., 1899.

4. Ranson, S. W.: (*a*) The Tract of Lissauer and the Substantia Gelatinosa Rolandi, Am. J. Anat. **16**:97-126, 1914; (*b*) footnote 2.

5. Massazza, A.: La citoarchitettonica del midollo spinale umano, Arch. anat., histol. et embryol. **3**:115-192, 1924.

6. Bok, S. T.: Das Rückenmark, in von Möllendorff, W., Editor: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, Vol. 4, pp. 478-578.

7. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, Vol. I, New York, The Macmillan Company, 1936.

preparations of spinal cords of the newborn cat and human baby. The formula used in the Golgi method is a modification of the procedure used by Fox and co-workers [8] and Pearson.[9]

In brief, the cerebral and cerebellar cortex, brain stem, and spinal cord can be prepared in the following manner:

The tissue is fixed in 10% formalin. Material fixed for several months gives the best results.

Thin slices (2 to 3 mm. thick) of the central nervous system are placed in 4 gm. of zinc carbonate and 4 gm. of chromic acid dissolved in 96 cc. of distilled water and 4 cc. of formic acid for three days. The sections are removed, blotted, and suspended by a thread in a 0.75% silver nitrate solution for three to six days. This solution is changed several times. The slices are dehydrated rapidly, cleared in xylol, embedded in low melting-point paraffin, and sectioned. Sections are mounted and covered with a mounting medium. Plastic cover glasses may be used. All glassware should be chemically clean.

The measurements of cells were made according to the method used by Conel [10] in his monograph on the cortex of the newborn baby. The cell bodies are measured by calibrating the spaces on a glass ocular micrometer with a stage micrometer. The length and greatest breadth of a cell body of a neuron are indicated, for example, as 10 by 8 μ. The limits of the variations in the sizes of cells are shown in this manner, 10 by 6 to 16 by 10 μ. This would indicate that the cell bodies range in size from 10 μ long by 6 μ wide to 16 μ long by 10 μ wide. Owing to the shrinkage of the cells at the time of fixation and other factors which could not be controlled, these measurements must be regarded as only approximate.

OBSERVATIONS

Gelatinous Substance of the Human Spinal Cord.—Because of its gelatinous or translucent appearance in fresh unfixed specimens, the gray matter at the apex of the dorsal horns of the spinal cord is known as the gelatinous substance. This structure is usually associated with the name of the Italian anatomist Luigi Rolando (1773-1831); in the "Basle Anatomical Nomenclature" it is listed as the substantia gelatinosa Rolandi. The gelatinous appearance is due to the scarcity of large neurons and to the presence of a dense network of dendrites and many unmyelinated and finely myelinated fibers, which pass among the small cells of this region. Large myelinated fibers from the dorsal roots also enter the gelatinous substance, but they are thought to pass through it, without synaptic connections, and into the underlying gray matter. There are also numerous neuroglia cells. The gelatinous substance extends throughout the length of the spinal cord and is continuous with the nucleus of the spinal tract of the fifth cranial nerve in the medulla oblongata. The size and shape of this area at the various levels of the spinal cord are illustrated in the atlases on the nuclei of the human spinal cord by Bruce [11] and Jacobsohn.[12] Jacobsohn refers to this area as the nucleus sensibilis proprius. It is held by many investigators that the constituent cells are small neurons whose short dendrites do not extend beyond the limits of the gelatinous substance and whose axons terminate either within it or only a short distance away.

8. Fox, C. A.; Ubeda-Purkiss, M.; Ihrig, H. K., and Biagioli, D.: Zinc Chromate Modification of the Golgi Technique, Anat. Rec. **106**:303, 1950.

9. Pearson, A. A.: A Modification of the Golgi Technique, Anat. Rec. **109**:405-406, 1951.

10. Conel, J. L.: Postnatal Development of the Human Cerebral Cortex, Vol. I, The Cortex of the Newborn, Cambridge, Mass., Harvard University Press, 1939.

11. Bruce, A.: A Topographical Atlas of the Spinal Cord, London, Williams & Norgate, 1901.

12. Jacobsohn, L.: Über die Kerne des menschlichen Rückenmarkes, Berlin, Verlag der Königlich-bayerische Akademie der Wissenschaften, in Kommission bei Georg Reimer, 1908.

Favorable Golgi preparations of the spinal cord of human babies confirm many of these assumptions. The great majority of the cells in the gelatinous substance are small multipolar neurons (Fig. 1). As a rule, their cell bodies are a little larger than a red blood corpuscle and are round, oval, fusiform, or triangular. The limits of the variations in the sizes of these cells in the spinal cord of an infant are approximately 10 by 6 to 16 by 10 μ.

The dendrites of the cells spread out in all directions and branch freely. Some cells show a tendency to have a dorsoventral polarity; this polarity, however, may be more apparent than real. Most of the cells are hidden in the very dense neuropil, of which their dendrites form a conspicuous part. It is only the occasional isolated cell whose processes can be seen distinctly. According to Ramón y Cajal,[1] the dendrites of these cells in the newborn dog tend to spread out in a plane which is

Fig. 1.—Representative small neurons selected at random in the gelatinous substance of the spinal cord of an infant. From transverse sections of Golgi preparations; approximately × 268.

parallel to the dorsolateral surface of the spinal cord. Earle [13] noted that these cells are oriented in a longitudinal plane. A fuller spread of the dendrites of the cells would be shown in longitudinal rather than in transverse sections of the spinal cord.

The axons of the cells are fine and difficult to demonstrate. In my material only an occasional cell showed a process which could be identified as an axon. The few axons observed gave off collateral branches and were soon lost in the dorsal horn. Ramón y Cajal [14] traced some of the axons into Lissauer's zone, into the fasciculus cuneatus, and into the ground bundles adjoining the dorsal horn. Cajal made most of these observations on chick embryos.

13. Earle, K. M.: Tract of Lissauer and Its Possible Relation to the Pain Pathway, J. Comp. Neurol. **96**:93-111, 1952.

14. Ramón y Cajal, S.: Histology, revised by J. F. Tello-Múñoz, translated from the 10th Spanish Edition by M. Fernán-Núñez, Baltimore, William Wood & Company, 1933.

In the dog [7] the gelatinous substance of one side may be continuous with that of the other side. The gray columns are said to be covered dorsally by a cortex-like gelatinous layer. A similar cortex-like structure in the human infant is illustrated in Figure 4.

Nucleus Proprius of the Human Spinal Cord.—The nucleus proprius of the dorsal horn is also referred to as the proper sensory nucleus, the nucleus magnocellularis centralis, the nucleus spinothalamicus, the nucleus centrodorsalis, the nucleus of Waldeyer, and the dorsal funicular cells. This column of cells is located just beneath the gelatinous substance of Rolando and is found at all levels of the spinal cord. As one would expect, these cells are more numerous in the cervical and lumbar enlargements of the spinal cord.[15] They are medium-sized to large multipolar neurons. The majority of the cells bodies are triangular or spindle-shaped. Some can only be described as being large multipolar neurons. The smallest are somewhat larger than the neurons of the gelatinous substance, while the largest may

Fig. 2.—Typical neurons of the nucleus proprius immediately adjoining the gelatinous substance of the dorsal horn of the spinal cord of an infant. From transverse sections of Golgi preparations; approximately × 168.

approach the size of the smaller ventral horn cells. The range in the sizes of these cells in the spinal cords of a human baby is roughly 20 by 15 to 60 by 32 μ. Cajal's [1] Figures 121 and 148 beautifully illustrate these cells in the spinal cord of the newborn cat and of the chick embryo.

The neurons of this cell column have coarse, freely branching dendrites, which extend in all directions. Small, spine-like processes are numerous on their many dendrites. These are thought to be parts of synaptic endings. The cells show a tendency toward polarity, in spite of the fact that they are multipolar neurons. The dorsally directed dendrites pass into the gelatinous substance, where they branch freely and are embedded in the dense neuropil of that region. The dendrites from the ventral portions of their cell bodies ramify in the gray matter beneath the gelatinous substance.

15. Massazza.[5] Bok.[6] Jacobsohn.[12]

The neurons immediately adjoining the gelatinous substance of Rolando are more apt to be of medium size (Fig. 2). Their dorsally directed dendrites extend into the gelatinous substance, where their branching appears to be restricted to a rather narrow region. They approach the dorsal margin of the gelatinous substance but do not pass beyond it, either into Lissauer's zone or into the posterior funiculus.

The cells just beneath those bordering on the gelatinous substance are of medium to large size (Figs. 3 and 4). Their dorsally directed dendrites pass among the neurons of the nucleus proprius, which lie dorsal to them, before reaching the gelatinous substance. On reaching the latter, their dendrites spread out into a wider

Fig. 3.—Three neurons of the nucleus proprius deep to those shown in Figure 2, which border on the gelatinous substance. A few of the small neurons and a small area of the dense neuropil of the gelatinous substance are shown. The broken line indicates the boundary between the gelatinous substance and the nucleus proprius. A neuron similar to those in Figure 2 is shown on the extreme left, just below the border of the gelatinous substance. From transverse sections of Golgi preparations of the spinal cord of an infant; approximately × 168.

zone, which would include the dendritic spread of several of their dorsal neighboring cells. Little can be said concerning the exact connections of the ventral and side dendrites of these neurons other than that they come into contact with the other cells of this nucleus and with cells toward the center of the gray columns. It seems unlikely that they pass as far ventrally as the cell bodies of the anterior horn neurons, although this may occur.

Axons of the cells of the nucleus proprius were difficult to find in my material. Those which could be demonstrated were fine fibers which came directly off the cell

body or off a large ventral dendrite. These fibers usually ran ventrally through the field for a short distance and were lost. The consensus is that these neurons send their axons through either the anterior or the posterior white commissure and into the anterolateral funiculus of the opposite side. It is also claimed that the axons of some cells enter the anterolateral funiculus of the same side.[6]

Pericornual Cells of the Human Spinal Cord.—Scattered large nerve cells occur in the posterior, medial, and lateral margins of the gelatinous substance.[15] These cells are also referred to as the marginal cells, the posteromarginal nucleus, and the pericornual magnocellular cell column. They do not form a continuous layer, as only a few of them are present at a given level. A small number of them were

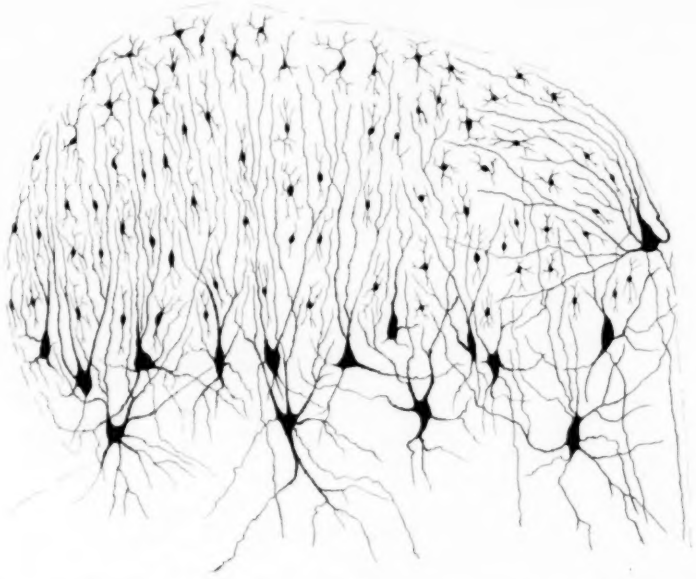

Fig. 4.—A composite semischematic drawing showing the relation of the gelatinous substance to the neurons of the nucleus proprius and the pericornual cells. From transverse sections of Golgi preparations of the left side of the spinal cord of an infant.

impregnated by the Golgi method in my material, and these were located in the medial margin of the gelatinous substance. They are large multipolar neurons (Figs. 4 and 5) with coarse, freely branching dendrites, which spread out laterally into the gelatinous substance. Earle [13] reports that they appear larger in longitudinal sections of the cat's spinal cord. Their dendrites are richly covered with gemmules or spiny excrescences and appear to be limited in their spread to the region of the gelatinous substance. The dendrites arising from the medial side of these cells either are short processes or turn laterally into the gelatinous substance close to the cell body. A fine process, which was thought to be an axon, extends ventrally from some of these cells. Unfortunately, the axons could be followed for only a short

distance. They are usually said to enter the lateral funiculus and to bifurcate there into ascending and descending fibers, which form intersegmental connections. Bok [6] considered them to be association neurons of the posterior horn. Since only a few of these cells were impregnated in my material, it is not possible to give a reliable estimate as to their range in size and shape. The available data would indicate that these cells are roughly 40 by 30 to 60 by 40 μ in the spinal cord of the human baby. Cajal's Figures 148 [1] and 333 [14] illustrate these cells in the spinal cord of chick embryos.

Another type of cell observed in the gelatinous substance, often in its margin, is smaller and spindle-shaped. Its dendrites arise mainly from the two ends of the cells, which point dorsally and ventrally. The spread of the dendrites again appears to be restricted to the gelatinous substance. A short process resembling an axon was sometimes evident. Only a very few cells of this type were observed, and it is not possible to give an estimate of their average size. Those observed were about 40 to 60 by 10 μ.

Fig. 5.—Pericornual cells from the medial margin of the gelatinous substance of the left side of the spinal cord of an infant. From transverse sections of Golgi preparations; approximately × 168.

Nerve Endings in the Gelatinous Substance of the Cat.—The fibers passing into the posterior gray columns of the spinal cord were better shown in my Golgi material of the newborn cat than in the human material. Numerous fibers can be seen leaving the posterior funiculus and Lissauer's zone and extending down into the gray matter of the spinal cord. Many of the coarser and more conspicuous groups of fibers by-pass the gelatinous substance by coursing on its medial and lateral sides. Some pass directly through it to reach the deeper cells of the posterior gray columns. Osmic-acid preparations reveal that a large number of these are myelinated fibers. Some of them end in the dense entanglement of nerve fibers around the cells of the nucleus proprius.

Many of the finer fibers terminate in the gelatinous substance. Several types were observed (Fig. 6). Some follow the medial or lateral margin of the gelatinous substance and, on reaching its under surface, turn dorsally into that area for a short distance and are lost. These fibers branch and give off fine collaterals into this region. Cajal's [1] Figure 121 shows the intricate branching of these fibers in the spinal cord of the newborn cat. Fibers of a similar type pass directly through the gelatinous substance and, on reaching its ventral margin, turn dorsally and again

enter the gelatinous substance, in which they then branch and appear to end. Many fine fibers enter the dorsal margin of the gelatinous substance and lose themselves in the deeper portions of that area. The initial branching of some of these fibers takes place immediately under Lissauer's zone; they then send collaterals into the deeper portions of the gelatinous substance. Some fibers bifurcate at various levels and give off collaterals as they pass ventrally (Fig. 6). Occasionally a fine fiber can be seen terminating in a small nodule on a dendrite or on the cell body of a neuron of the nucleus proprius. These fibers appear to give off the majority of their branches in the ventral zone of the gelatinous substance. It is in this region that the dendrites of the cells of the nucleus proprius of the dorsal horn are most numerous.

Neuropil.—It is not possible to illustrate or adequately to describe the extremely dense neuropil of the gelatinous substance. Favorable cross sections of Golgi

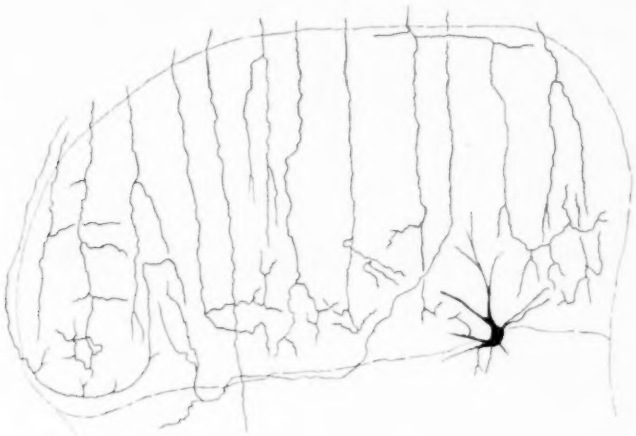

Fig. 6.—A composite semischematic drawing showing the position and course of some of the fine fibers which enter the gelatinous substance from Lissauer's zone. From transverse sections of Golgi preparations of the left side of the spinal cords of newborn cats; approximately × 145.

material reveal in the gelatinous substance a close meshwork of branching fibers in which the dendrites of the pericornual cells and the dorsal dendrites of the cells of nucleus proprius are embedded. Sagittal sections of the spinal cord show that it includes many fibers which course in a longitudinal plane. These fibers have many varicosities, branch repeatedly, and give off fine collaterals, many of which terminate in small end-knobs.

COMMENT

The observations described here have been limited to the gelatinous substance of Rolando and the neighboring cells whose dendrites extend into the area. My Golgi material gives a clearer picture of the arrangement of the neurons in the posterior horn in the human spinal cord than has been previously described and offers a basis for comparison with lower mammals.

It has been shown that painful impulses are received by naked nerve terminals in the skin,[16] and it is believed that similar endings mediate pain sense in other parts of the body. These naked terminals result from the repeated terminal branching of myelinated and unmyelinated fibers. Pain can be aroused from the deeper layers of the epidermis and the superficial layers of the dermis through superficial and deep nerve plexuses. Both of them are subserved by the same nerve apparatus. These plexuses are beautifully illustrated in Figure 13 of Woollard and associates [16] and in Figure 112 of Larsell.[17] The receptors for pain sense, like those for pressure, heat, cold, and touch sensibility, are represented in the skin in a punctate form of distribution. For example, on the back of the human hand, a superficial nerve net from a single fiber covers an area which is roughly 0.75 cm. in diameter.[18] Encapsulated receptors, e. g., Meissner's corpuscle and Krause's end-bulbs, are supplied, in addition to their principal nerve fibers, by "accessory" nerve endings which are morphologically similar to the free nerve endings subserving pain.[16] According to Walshe,[19] these "accessory" nerve endings appear to endow the encapsulated end-organ with pain sensibility when supramaximally stimulated.

Pain impulses are believed to be carried through myelinated and unmyelinated fibers at various rates of speed.[20] Slow pain impulses are carried in unmyelinated C-fibers, in which conduction is 1 to 2 meters per second, and fast pain impulses, in meylinated A-fibers, in which conduction is 15 to 90 meters per second. There is evidently a range between the velocities of A- and C-fibers which is not occupied by pain impulses. Gasser [20a] and others have pointed out that there is a double pain response to a single stimulus, e. g., a needle prick. The slower pain impulses, carried by the C-fibers, do not reach the centers of consciousness by the time the pain is first felt by reason of the more rapidly conducting A-fibers.

In tabes dorsalis, the most pronounced degenerative changes found in the dorsal roots of the spinal nerves are in the large myelinated fibers. If there is a degeneration of the small unmyelinated fibers, which contribute to the formation of Lissauer's zone, it has not been established.[21] Pochin [22] concluded, from a series of studies on the perception of pain, that there is a delay in pain perception in some cases of tabes dorsalis due to a defect in the group of fibers which conduct fast pain. This delay of pain perception in tabes is thought to be due to the slow peripheral conduction of pain impulses, which is at a rate corresponding to that of known slowly

16. Woollard, H. H.; Weddell, G., and Harpman, J. A.: Observations on the Neurohistological Basis of Cutaneous Pain, J. Anat. **74**:413-440, 1940.

17. Larsell, O.: Anatomy of the Nervous System, Ed. 2, New York, Appleton-Century-Crofts, Inc., 1951.

18. Weddell, G.: Pattern of Cutaneous Innervation in Relation to Cutaneous Sensibility, J. Anat. **75**:346-367, 1941.

19. Walshe, F. M. R.: Anatomy and Physiology of Cutaneous Sensibility: A Critical Review, Brain **65**:48-112, 1942.

20. (*a*) Gasser, H. S.: Pain-Producing Impulses in Peripheral Nerves, A. Res. Nerv. & Ment. Dis. Proc. **23**:44-62, 1943. (*b*) Wolff, H. G., and Wolf, S.: Pain, American Lectures in Physiology, Springfield, Ill., Charles C Thomas, Publisher, 1948.

21. Forbus, W. D.: Reaction to Injury: Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents, Baltimore, Williams & Wilkins Company, 1943.

22. Pochin, E. E.: Delay of Pain Perception in Tabes Dorsalis, Clin. Sc. **3**:191-196, 1938.

conducting pain impulses in C-fibers from normal skin. The delay in tabes is most likely due to the degeneration of the large, fast-conducting pain fibers without a corresponding defect in the small, slow-conducting fibers, and not to an abnormal slowing of the pain impulses in a diseased region.

The work of Ranson [4] and others has demonstrated that the fibers of the dorsal roots of the spinal nerves separate into smaller lateral and larger medial divisions as they enter the spinal cord. The lateral division has been shown to be composed mainly of small myelinated and unmyelinated fibers, which enter only the medial part [12] of Lissauer's zone. These fibers stand in contrast to the medial division of the dorsal root, which is made up largely of coarse myelinated fibers. A few large myelinated fibers, however, can also be traced from the dorsal root into Lissauer's zone (Fig. 7). Inside the cord each dorsal root fiber divides [1] into an ascending and a descending branch, both of which are of limited length in Lissauer's zone. These exogenous fibers account for only 25% or less of the total fibers in this zone. The remainder of the fibers in Lissauer's zone (about 75%) [13] are endogenous, arising from cells located in the posterior gray columns. These course in a longitudinal direction, for the most part. Thus, the fibers in Lissauer's zone are in part endogenous and in part exogenous. According to Earle,[13] this zone is composed of short fibers which do not extend over more than one or two segments. Barker,[3] Ranson,[4] and Earle [13] have summarized the earlier work on this subject.

Ranson [4a] has described two layers in the gelatinous substance and a third, or intermediate, layer at the border between it and the underlying gray substance. According to him, the superficial layer of the gelatinous substance, the stratum zonal, contains many unmyelinated fibers and a few myelinated fibers. This layer lies next to Lissauer's zone, and between the two there is a free exchange of fibers. The second layer is the gelatinous substance proper. It contains a plexus made up almost entirely of unmyelinated fibers, which is somewhat less dense than the preceding layer. The third, or intermediate, layer, at the ventral boundary of the gelatinous substance, is a dense plexus of fibers, most of which are unmyelinated. Ranson [4a] points out that the majority of these fibers have a vertical course. The three layers described by Ranson are not distinct in my Golgi material. Longitudinally coursing fibers are prominent in some of my sagittal sections, and these probably correspond to the third layer of Ranson. Bok [6] considered the gelatinous substance the great association organ of the posterior horn.

Ranson [23] demonstrated that bilateral destruction of Lissauer's zone and the gelatinous substance at the level of the first lumbar segment of the cat's spinal cord did not interfere with the perception of pain in the hindlimbs, but it did abolish the pressor vasomotor reflex on stimulation of the sciatic nerve. This he regarded as evidence that Lissauer's zone and the gelatinous substance of Rolando form a path for intersegmental conduction of the afferent impulses involved in reflex vasoconstriction due to painful stimulation of the sciatic nerve.

Subsequently, Ranson and Billingsley [24] demonstrated, in experiments on anesthetized cats, that when the fibers from the lateral division of the dorsal root of a

23. Ranson, S. W.: Unmyelinated Nerve-Fibers as Conductors of Protopathic Sensation, Brain **38**:381-389, 1915.

24. Ranson, S. W., and Billingsley, P. R.: Conduction of Painful Afferent Impulses in the Spinal Nerves, Am. J. Physiol. **40**:571-584, 1916.

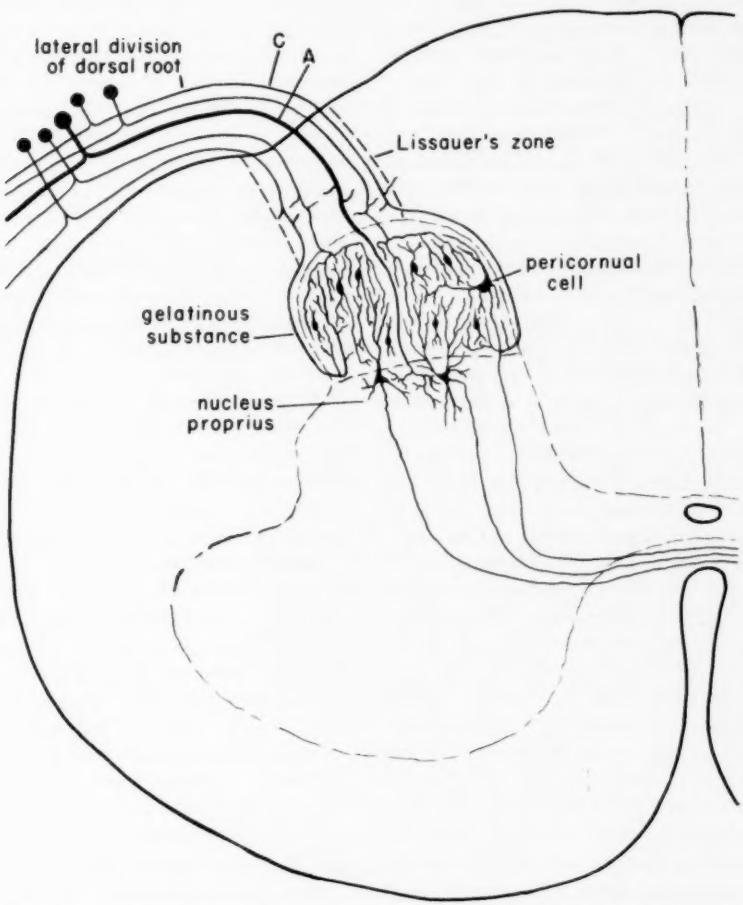

Fig. 7.—A schematic drawing of a transverse section of a human spinal cord showing the relation of the fibers of the lateral division of the dorsal root of a spinal nerve to the neurons in the dorsal horn. The A-fiber represents the large myelinated fibers which pass through (or around) the gelatinous substance to synapse with the neurons in nucleus proprius. The other fibers shown in the dorsal root are the more numerous C-fibers, i. e., the fine myelinated or unmyelinated fibers which end in the gelatinous substance. The small cells of the gelatinous substance are represented as internuncial neurons. A pericornual cell and cells of the nucleus proprius are shown sending axons across the midplane on their way to the lateral spinothalamic tract. Other paths of these neurons are outlined in the text.

spinal nerve are cut, pain reflexes, such as struggling, acceleration of respiration, and rise in blood pressure, obtained from stimulation of the intact root, are eliminated at once. A cut involving the medial division of the dorsal root had little or no effect on pain reflexes. Thus, Lissauer's zone and the gelatinous substance have been shown to be important links in the reception and conduction of pain impulses. Certain pain impulses pass to higher centers by way of the spinothalamic tract and find expression as conscious pain, while others ascend and descend in the spinal cord, producing pain reflexes.[23]

The relation of the dorsal root fibers to the gelatinous substance is further illustrated in the experiments of Szentagothai and Kiss.[25] When a small lesion was placed in the dorsorostromedial sector of the second cervical spinal ganglion, there followed degeneration of a large number of the fibers of the dorsal branch of that nerve. Degenerative changes were also present in the fine intercellular terminal plexuses in the lateral half of the gelatinous substance, while the medial half remained intact. In the same manner, the ventrocaudolateral sector of the second cervical spinal ganglion was found to contribute fibers mainly to the ventral branch of that spinal nerve, and the intercellular terminal plexuses within the gelatinous substance were found to degenerate only in the medial half. These experiments suggest that the dorsal part of the dermatome is represented in the lateral half, and the ventral part of the dermatome in the medial half, of the gelatinous substance.

As already described, the finely myelinated and unmyelinated dorsal root fibers terminate in the gelatinous substance (Figs. 6 and 7). Here they can come into synaptic relation with the pericornual cells, the constituent cells of the gelatinous substance, and the dorsal dendrites of the cells of the nucleus proprius. The axons of the cells of the gelatinous substance appear to end in synaptic relation with the pericornual cells and the cells of the nucleus proprius. The evidence at hand indicates that the impulses coming in through finely myelinated and unmyelinated fibers of the dorsal root are largely concerned with the conduction of pain, and possibly temperature sensibility. This is very likely the slow type of pain impulses which is conducted in the small C-fibers at 1 to 2 meters per second. Thus, in the conduction of slow pain impulses, the small fibers of the dorsal root are neurons of the first order; the constituent neurons of the gelatinous substance, neurons of the second or higher order, and the pericornual neurons and neurons in the nucleus proprius, neurons possibly of the second, but more likely of the third, or even a higher, order.

Some of the coarser dorsal root fibers pass around or through the gelatinous substance, apparently without synapsing in it, and end in arborizations in the nucleus proprius. These coarse dorsal root fibers are neurons of the first order, and the neurons of the nucleus proprius in this case would be neurons of the second order (Fig. 7). This is probably the conduction path for fast pain impulses, which are carried in the coarser A-fibers, at 15 to 90 meters per second, directly to the cells of the nucleus proprius, without synapsing with internuncial neurons in the gelatinous substance. In fast pain conduction not only coarser fibers, but probably fewer neurons, are involved.

25. Szentagothai, J., and Kiss, T.: Projection of Dermatomes on the Substantia Gelatinosa, Arch. Neurol. & Psychiat. **62**:734-744, 1949.

The general consensus is that a spinothalamic tract arises from the cells in the posterior gray column which lie just ventral to the gelatinous substance. For this reason, these cells have often been referred to as the nucleus spinothalamicus. In studies based on the cell changes in the spinal cord after anterolateral chordotomy, Foerster and Gagel [26] noted alterations in the large cells about the posterior horns without changes in the gelatinous substance or the rest of the spinal cord. They divided the large cells around the gelatinous substance, according to their position, into the basal, pericornual, and apical groups. Unilateral chordotomies resulted in changes in these large cells around the posterior horns on both sides, the changes being more pronounced, however, on the contralateral side. After anterolateral chordotomy, Kuru [27] found that the degree of the changes in the pericornual and apical cells was closely related to the severity of the sensory disturbance (appreciation of pinprick), while the degree of the alterations in the basal cells showed no such relationship. He concluded that the apical and pericornual cells were the cells of origin of the spinothalamic and spinotectal tracts. Walker [28] pointed out that Kuru's conclusions are open to criticism in that disturbances in temperature and touch sensibility were not considered, and he questioned the conclusion that the pericornual and apical groups of cells were the only source of the spinothalamic fibers.

While the pericornual cells have been regarded as association neurons of the posterior gray columns,[6] there is Kuru's [27] evidence that their axons help form the spinothalamic pathways. It is very likely that the majority of the medium-sized and large neurons (Figs. 4 and 7), whose dendrites spread out into the gelatinous substance, contribute fibers to the spinothalamic tracts. The small cells of the gelatinous substance probably serve as internuncial neurons between dorsal root fibers and other neurons, in particular, the pericornual cells and the cells of the nucleus proprius. The small size of the cells of the gelatinous substance and the length of the axons necessary to reach the thalamus by way of the spinothalamic tract would make it unlikely that they are the origin of this long conduction path. It has been pointed out that the pericornual cells and the cells of the nucleus proprius are in synaptic relation with terminals of dorsal root fibers and axons of the cells of the gelatinous substance, and that they probably serve as neurons of the second, third, or even higher order.

Olszewski [29] has shown that only the nucleus caudalis of the nucleus of the spinal trigeminal tract has a cell arrangement similar to that in the head of the posterior gray column of the spinal cord. The nucleus caudalis is considered by

26. Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen: Eine klinisch-patho-physiologisch-anatomische Studie, Ztschr. ges. Neurol. u. Psychiat. **138**:1-92, 1932.

27. Kuru, M.: Die Veränderung im Zentralnervensystem bei den 2 Fällen von "partieller" Chordotomie: Ein Beitrag zur Frage der Ursprungszellen des Tractus spinotectalis et -thalamicus, Gann **32**:1-25, 1938.

28. Walker, A. E.: The Spinothalamic Tract in Man, Arch. Neurol. & Psychiat. **43**:284-298, 1940.

29. Olszewski, J.: On the Anatomical and Functional Organization of the Spinal Trigeminal Nucleus, J. Comp. Neurol. **92**:401-413, 1950.

him to be the only cranial-nerve nucleus concerned with the conduction of pain and temperature impulses from the face.

The whole problem of the anatomy, physiology, and psychology of pain has been reviewed by Livingston.[30] This author has described fast pain as being more vivid, less persistent, and more readily localizable, whereas slow pain is diffuse in character and difficult to localize exactly. It is probable that the fast pain impulses, which are conducted over coarse fibers directly to neurons giving rise to the spinothalamic tract, would be better localized than the slower pain impulses, carried by the finer fibers which terminate centrally in the diffuse neuropil of the gelatinous substance of Rolando and which peripherally are arranged [16] in a plexiform, interlocking system of fine fibers bearing free nerve endings.

If it can be assumed that visceral pain is carried largely by small fibers of the C-group, then its more diffuse character can be explained in a similar manner. Histological evidence, as illustrated in Figures 6 and 7, confirms the usual physiological interpretation that some visceral afferent fibers converge with cutaneous pain afferent fibers,[31] both ending together in the diffuse neuropil of the gelatinous substance of Rolando, where their impulses are transmitted to the same neurons of the spinothalamic tract. The impulses from the skin and the viscera are then carried to the brain, where they are interpreted, in terms of past experience, as having come from the skin.

SUMMARY

This study on the gelatinous substance of the posterior gray columns of the spinal cord is based primarily on Golgi preparations of human infants and newborn cats. The gelatinous substance is composed mainly of small multipolar neurons whose processes are limited to that region. The pericornual cells are large multipolar neurons scattered in the posterior, lateral, and medial margins of the gelatinous substance. Their coarse, freely branching dendrites spread out in the gelatinous substance. The cells lying under the gelatinous substance constitute the nucleus proprius. The cells lying closest to the gelatinous substance are medium-sized to large multipolar neurons. Their dorsally directed dendrites extend into a rather narrow zone of the gelatinous substance. The deeper cells of this nucleus are often a little larger, and the spread of their dorsal dendrites may include the dendritic zone of several of their dorsal neighbors. The ventrally directed dendrites are lost in the adjacent gray matter. The axons of the above cells could not be followed for any great distance.

Numerous fibers leave the posterior funiculus and Lissauer's zone and enter the posterior gray columns. Many of the coarser fibers circumvent the gelatinous substance by passing on its medial or its lateral side. Some pass directly through it to reach the deeper cells of the posterior gray columns. Many of the finer fibers terminate in the gelatinous substance. Several types of these were observed. One type passes along the lateral or the medial margin of the area and then turns dorsally into the gelatinous substance, where it is lost. Another passes directly through the area and then turns dorsally into the gelatinous substance. Some fibers bifurcate as

30. Livingston, W. K.: Pain Mechanisms: A Physiologic Interpretation of Causalgia and Its Related States, New York, The Macmillan Company, 1943.

31. Ruch, T. C.: Visceral Sensation and Referred Pain, in Howell's Textbook of Physiology, Ed. 16, edited by J. F. Fulton, Philadelphia, W. B. Saunders Company, 1949, Chap. 19, pp. 360-374.

they pass ventrally. Others divide close to the dorsal margin and send off branches. All these fibers appear to give off the majority of their terminal branches in the ventral zone of the gelatinous substance. It is in this region that the dendrites of the cells of the nucleus proprius of the dorsal horn are most numerous.

The evidence suggests that small pain-conducting fibers from Lissauer's zone, ending in the gelatinous substance, relay their impulses through one or more intercalated neurons in this substance, to the pericornual cells and to the cells of the nucleus proprius, which, in turn, give rise to the lateral spinothalamic tract. It is unlikely that any fibers of the lateral spinothalamic tract arise directly from the small neurons of the gelatinous substance.

Larger fibers that penetrate or by-pass the gelatinous substance also end in synaptic relation to neurons of the nucleus proprius. Some of these, at least, may be fast pain-conducting fibers of neurons of the first order. In this case the neurons of the nucleus proprius would be of the second order. The probability is that in fast pain conduction not only coarser fibers but also fewer neurons are involved.

BLOOD EOSINOPHILES IN ALCOHOLIC STATES

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IN RECENT reports Smith [1] has proposed the theory that alcoholism is a metabolic disease associated with deficient adrenocortical function. A similarity between Addisonian crises and delirium tremens was implied. The author expressed the opinion that chronic alcoholism and/or repeated alcoholic bouts lead to various stages of adrenocortical insufficiency. On this basis, cortisone and corticotropin were used in the treatment of acute alcoholic states, delirium tremens, and other alcoholic conditions, with favorable results. Similar views have been expressed by Tintera and Lovell.[2]

As Bowman [3] indicated recently, there have been no further contributions in the literature tending to confirm or disprove this interesting theory.[3a] Accordingly, it seemed desirable at this point to report the preliminary results of an investigation in this area which we have conducted during the past year or more.

It is generally accepted that the response of circulating eosinophiles to the injection of epinephrine constitutes one of the methods of evaluating adrenocortical function. The purpose of this study, then, was to evaluate adrenocortical function in alcoholic patients by measuring the reduction in circulating blood eosinophiles following the subcutaneous injection of epinephrine.

MATERIAL AND METHODS

The procedure was performed on a series of unselected, although not entirely consecutive, alcoholic patients admitted to the Fairfield State Hospital during the past 12 to 15 months. There were 157 patients in the series—140 men and 17 women. The group was divided almost equally between persons suffering from acute alcoholic psychoses, namely, delirium tremens or acute hallucinosis, and patients with other conditions, such as "alcoholism without psychosis," chronic deterioration, Korsakoff's syndrome, or "other states," as indicated in the official diag-

1. Smith, J. J.: A Medical Approach to Problem Drinking, Quart. J. Stud. Alcohol **10**:251, 1949; Treatment of Acute Alcoholic States with ACTH and Adrenocortical Hormones, ibid. **11**:190, 1950.

2. Tintera, J. W., and Lovell, H. W.: Endocrine Treatment of Alcoholism, Geriatrics **4**:274, 1949. Lovell, H. W., and Tintera, J. W.: Hypoadrenocorticism in Alcoholism and Drug Addiction, ibid. **6**:1, 1951.

3. Bowman, K.: Alcohol; Geriatrics: Review of Psychiatric Progress 1951, Am. J. Psychiat. **108**:529, 1952.

3a. Since submission of this article for publication, two papers on this subject have been published: Dowden, C. W., and Bradbury, J. T.: Eosinophil Response to Epinephrine and Corticotropin: Studies in Alcoholics and Nonalcoholics, J. A. M. A. **149**:725, 1952. Mann, N. M.: Hypoadrenalism and the Alcoholic: Preliminary Report, Quart. J. Stud. Alcohol **13**:201, 1952.

nostic nomenclature. There were 80 patients in the first group and 77 in the second. The patients ranged in age from 21 to 76, with the following age distribution by decades: 20 to 29 years, 10; 30 to 39 years, 42; 40 to 49 years, 65; 50 to 59 years, 22; 60 to 69 years, 17; 70 to 79 years, 1. The initial eosinophile count was performed on fasting patients at approximately 8:30 a. m.; 0.3 cc. of 1:1,000 epinephrine hydrochloride was injected subcutaneously, and the eosinophile count was repeated four hours later. The first test was done usually within 24 to 48 hours after the patient's admission to the hospital. In addition, a second test was performed approximately 15 days later on those patients who were still hospitalized. We were able to perform a second test on 126 patients. In the majority of instances Hinkleman's solution was used as the diluent in the enumeration of eosinophiles, as it was found to be slightly superior to other solutions. The total leucocyte count was also made routinely at the time of the first test.

RESULTS

Results of the initial epinephrine-eosinophile test are summarized in the accompanying Table.

It is evident that some reduction in eosinophiles occurred in 80.3% of the series; the decrease was 50% or greater in 77 patients, or 49.1% of the total group.

The problem of controls is, of course, a pertinent one in this, as in other, investigations. The theory that a reduction of 50% or more in circulating eosinophiles after the injection of epinephrine represents a "normal" response seems to

Change in Eosinophiles in 157 Alcoholic Patients Following Injection of 0.3 Cc. of Epinephrine Hydrochloride

	In-creased	Un-changed	Decreased								
			1-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%	70-79%	80-100%
No.	17	14	1	3	18	17	10	20	13	18	26
Percentage of total	10.8	8.9	0.6	1.9	11.5	10.8	6.4	12.8	8.3	11.5	16.5

have gained general acceptance. Thorn and co-workers,[4] particularly have emphasized this feature. A recent study by Fisher and Fisher [5] has contributed valuable information in this direction. These authors confirmed the presence of a normal diurnal variation in eosinophiles. However, reduction in eosinophiles following epinephrine was much greater and more consistent than the changes observed during normal diurnal variation. Nevertheless, it is noteworthy that only 52% of a group of 25 normal subjects exhibited a decline of 50% or more in eosinophiles four hours after the subcutaneous injection of 0.3 cc. of 1:1,000 epinephrine hydrochloride. Only 4.7% of the same group revealed a reduction of similar magnitude on the control day, when they did not receive epinephrine.

It is apparent that the results in our alcoholic patients were essentially similar to those recorded by Fisher and Fisher in their group of normal controls. Thus, 49.1% of our patients exhibited a decline of 50% or more in eosinophiles, as compared with 52% of the group studied by Fisher and Fisher. It might be indicated also that our technique closely paralleled that of Fisher and Fisher with respect to amount and mode of administration of epinephrine and method of dilution and enumeration of eosinophiles.

4. Recant, L.; Hume, D. M.; Forsham, P. H., and Thorn, G. W.: Studies on Effect of Epinephrine on Pituitary-Adrenocortical System, J. Clin. Endocrinol. **10**:187, 1950.

5. Fisher, B., and Fisher, E. R.: Observations on the Eosinophil Count in Man: Proposed Test of Adrenal Cortical Function, Am. J. M. Sc. **221**:121, 1951.

Comparison was also made of the results in the group with acute alcoholic psychoses and those in patients exhibiting other alcoholic conditions. No significant difference was found. Thus, 37 of 80 persons in the first group, or 46.3%, revealed a fall of 50% or more in eosinophiles, as compared with 40 of 77 patients, or 51.9%, in the second group. This difference is not statistically valid ($p = 0.60$).

Similar results were obtained in the second test, which was performed on 121 patients approximately two weeks after the first epinephrine-eosinophile test, by which time acute delirium or the hallucinatory state has subsided. Thus, 56 of 121 patients, or 46.3%, revealed a decline of 50% or more in eosinophiles following injection of epinephrine. There is no statistically significant difference between this result and that obtained on the first test, or that reported by Fisher and Fisher for normal control subjects.

The next area of interest was concerned with the actual numerical value of eosinophiles at the beginning of each test. There has been relatively little agreement concerning the limits of the "normal" eosinophile count. For example, Osgood [6] suggested 0 to 400 per cubic millimeter; Todd and Sanford,[7] 50 to 400, while Thorn and associates proposed 100 to 250 as the normal range of eosinophiles. In the study reported by Fisher and Fisher, only 115 of 238 initial eosinophile counts in fasting persons, or 47%, fell within Thorn's proposed normal range. On the basis of their findings, Fisher and Fisher suggested that, for clinical purposes, a normal range of 25 to 300 eosinophiles per cubic millimeter would seem optimal.

In general, fasting eosinophile counts in our alchoholic patients were somewhat lower than those found in normal controls. For example, 112 of our 267 initial counts, or 40%, were within Thorn's proposed normal range, as compared with Fisher and Fisher's 115 of 238 counts, or 47%. The chi-square formula indicates that this is probably a significant difference ($p = 0.06$). On the other hand, 84.5% of the initial counts in our patients were within the limits of 25 to 300 per cubic millimeter, the normal range suggested by Fisher and Fisher. The average initial eosinophile count in our alcoholic patients was approximately 20% lower than the average in the normal persons studied by Fisher and Fisher.

Apparently, it has long been recognized that mental disorder is accompanied by relative eosinopenia. A recent report by Altschule and associates [8] indicated that the majority of psychiatric patients studied by them revealed eosinophile counts which were in or below the "low normal" range. Approximately 50% of their patients with dementia praecox, manic-depressive psychosis, and involutional disorders had initial eosinophile counts below 100 per cubic millimeter and approximately 78% had counts below 200 per cubic millimeter. In our alcoholic patients, the initial eosinophile count was below 100 in 54.2% of the patients, and below 200 in 87.3%.

6. Osgood, E. E.: A Textbook of Laboratory Diagnosis, with Clinical Applications for Practitioners, Ed. 2, Philadelphia, The Blakiston Company, 1935.

7. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology, Ed. 10, Philadelphia, W. B. Saunders Company, 1943.

8. Altschule, M. D.; Siegel, E. P.; Restaino, R. M., and Parkhurst, B. H.: Blood Eosinophilic Leukocytes in Mental Disease, A. M. A. Arch. Neurol. & Psychiat. **67**:228, 1952.

COMMENT

The data described above would seem to indicate that there is no significant difference between the results of the epinephrine-eosinophile test in our alcoholic patients and those of normal controls, as recorded by Fisher and Fisher. These authors emphasized the presence of marked fluctuations or diurnal variations in the eosinophile count of normal subjects. Despite the fact that injection of epinephrine effected a relatively consistent decrease in circulating eosinophiles, reduction of at least 50% in eosinophiles was observed in approximately 50% only of their normal controls. Essentially similar results were obtained in this study on alcoholic patients. It might be indicated that it is difficult to estimate the duration in years of excessive alcoholic intake in this group of patients. However, it may be noted that all our patients exhibited alcoholic addiction of sufficient duration and severity to warrant commitment to a state hospital. As indicated, at the time of admission to the hospital, approximately half of the entire group suffered from acute alcoholic delirium or psychoses superimposed on chronic alcoholism or recurrent alcoholic bouts. It is noteworthy that the response of eosinophiles to epinephrine in these patients was essentially the same as in the remainder of the group, who, presumably, were experiencing less acute metabolic stress.

The response of eosinophiles to injection of epinephrine is presumed to be due to the following chain of reactions: Epinephrine stimulates the anterior hypothalamus, which, in turn, activates the pituitary body to produce corticotropin; this arouses the adrenal cortex to secrete 11,17-oxysteroids, one of whose effects is to decrease circulating eosinophiles. In view of the fact that our alcoholic patients exhibited an end-reaction to this circuit which was comparable to that observed in normal persons, it seems logical to assume that there is no defect in the hypothalamic-pituitary-adrenocortical system in alcoholic persons. It must be acknowledged, however, that this represents only one method of measuring adrenocortical integrity, although it is a method that has been used extensively in recent investigations of psychiatric patients.

As indicated above, Altschule and co-workers reemphasized the observation that eosinophile counts in psychiatric patients tend to be rather low and that clinical improvement is usually associated with a rise in the eosinophile count. Altschule concluded that these observations are consistent with the concept that psychoses and severe neuroses are associated with an increase in some adrenocortical functions and that recovery is associated with depression of these functions. In accordance with this concept, the relatively low initial eosinophile counts in our alcoholic patients would tend to point to an increase in some adrenocortical functions, rather than the converse.

SUMMARY

Approximately 50% of a series of alcoholic patients exhibited a decline of 50% or more in circulating eosinophiles following the subcutaneous injection of 0.3 cc. of 1:1,000 epinephrine hydrochloride. This corresponds satisfactorily with the results obtained by Fisher and Fisher in a group of normal controls. The initial eosinophile counts in these alcoholic patients were chiefly in the "low-normal" range. These data do not confirm the presence of deficient adrenocortical function in alcoholic patients.

Miss Florence Pease and Mr. Louis Faenza gave technical assistance.

CHOLESTEROL CHANGES IN SCHIZOPHRENIC PATIENTS DURING INSULIN THERAPY

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SEVERAL investigators have reported on blood cholesterol levels in schizophrenic patients receiving insulin coma therapy. Katzenelbogen and associates [1] reported values on several patients during and after a coma showing that in some subjects there was no change over a period of three hours. Changes in any one coma seemed to be minimal or variable. Randall and associate [2] reported that the total and free cholesterol increased during therapy and remained high for two weeks after treatment. Gottfried and Willner [3] tested a few patients before and after a course of insulin therapy and found no significant variation. Recently, Larue and co-workers [4] sampled patients at more frequent intervals during treatment and demonstrated a greater variability in those patients during the course of therapy than in schizophrenic patients not receiving treatment.

Unpublished data on 20 patients obtained by workers in this laboratory before, during, and after a course of insulin therapy showed essentially the same results, that is, variability of response, with a slight preference for an increase in blood cholesterol during a course of insulin therapy. Examination of these data revealed sufficient emphasis on an increase during insulin therapy to suggest further investigation; therefore, it was decided to take a small number of patients and sample them more frequently.

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Data for this paper were obtained with the technical assistance of Miss Jane Yarborough and Miss Barbara Moyer on patients at the neuropsychiatric division, Veterans Administration Center, Los Angeles.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Katzenelbogen, S.; Harms, H. E.; Wilmanns, R.; Barkoff, S.; Brody, M. W., and Hayman, M.: Insulin Treatment in Schizophrenic Patients: Clinical and Biochemical Studies, Am. J. Psychiat. **95**:793-797, 1939.

2. Randall, L. O., and Jellinek, E. M.: Physiological Studies in Insulin Treatment of the Acute Schizophrenic: Serum Lipids, Endocrinology **25**:105-110, 1939.

3. Gottfried, S. P., and Willner, H. H.: Blood Chemistry of Schizophrenic Patients Before, During and After Insulin Shock Therapy, Arch. Neurol. & Psychiat. **62**:809-817, 1949.

4. Larue, G. H.; Painchaud, C. A., and Nadeau, G.: Metabolic Variations in Schizophrenia, Canad. M. A. J. **62**:581-584, 1950.

METHOD

Control levels for total, ester, and free cholesterol were obtained on each patient before the initiation of insulin therapy. During the course of treatment, samples were taken three times a week—on Monday, Wednesday, and Friday. The blood was obtained just at the termination of the coma, prior to the intravenous injection of glucose. Cholesterol analyses were done by the method of Kanter and Goodman.[5] The course of treatment used at this hospital consisted of five successive days of insulin administration a week, with rather rapid increase in the dose of the drug until the first coma was produced, as recommended by Bond and Shurley.[6] Frequently, the insulin dose was reduced shortly after the first coma and adjusted to a level that continued to produce coma in the patient.

Samples were taken for one month to six weeks after the termination of insulin therapy. Eight patients were tested for a total period of four to five months. The curves of four of the eight patients, showing the total cholesterol, per cent ester cholesterol, and the insulin dose, are presented. The diagnosis by the "shock board," the summary of "coma data," and the psychiatrist's evaluation of the degree of improvement are indicated.

OBSERVATIONS

The fluctuations (Charts 1, 2, 3, and 4) were quite clearly greater during the course of therapy than either before or after the first post-treatment week. The per cent ester curve was relatively steady, indicating that both the free and the ester cholesterol content were changing. However, the most striking characteristic was that nearly all major increases occurred over the two-day week-end rest from therapy, and, concomitantly, that the sharp declines generally took place early during the week when insulin was being administered. This pattern was consistent for all patients tested, on nearly all weekly cycles. The drop during the week of coma treatments was usually at a minimum by Wednesday, with little further change on Friday. An increase was also present after the last insulin coma. This post-treatment peak was generally attained on the Wednesday following the last coma, that is, when Friday was the termination day, which was true of nearly every patient in this study. The return to lower levels was completed by the second or third week after therapy. Generally, the last decline was a slower, more tangential change than the decreases that occurred during a week of insulin coma treatments.

There were several occasions when the treatment was interrupted, owing to a national holiday. These occasions coupled with a week end meant four days without treatment. The increases that occurred were about the same as on two-day week ends. However, when the therapy was interrupted owing to illness of the patient (Chart 3), the typical increase did not usually occur.

The significance of these changes is not clear and is being further studied and correlated. Nonetheless, one is tempted to consider the possibility that the changes may be akin to some of the cholesterol changes seen with corticotropin administration. Conn[7] reported a sharp decrease in serum cholesterol in normal subjects given corticotropin. Possibly the drop during a week of therapy may be related to adrenal-cortex function. This suggestion led to the examination of eosinophile

5. Kanter, S.; Goodman, J. R., and Yarborough, J.: Determination of Free, Ester and Total Cholesterol Without Saponification, J. Lab. & Clin. Med. **40**:303-312, 1952.

6. Bond, E. D., and Shurley, J. T.: Insulin Therapy and Its Future, Am. J. Psychiat. **103**:338-341, 1946.

7. Conn, J. W.; Vogel, W. C.; Louis, L. H., and Fajans, S. S.: Serum Cholesterol: A Probable Precursor of Adrenal Cortical Hormones, J. Lab. & Clin. Med. **35**:504-517, 1950.

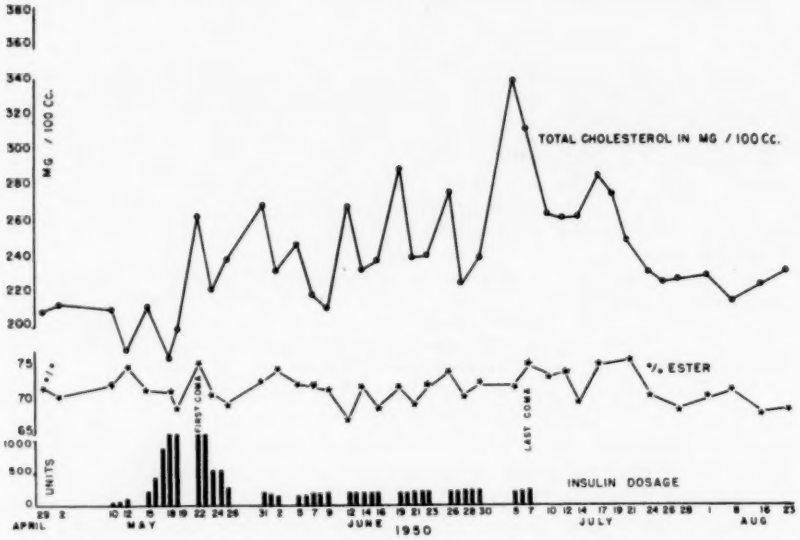

Chart 1.—R. W., with a diagnosis of schizophrenia, paranoid type, had 30 comas, 125 insulin treatment hours and 42 hours of unconsciousness, 27 hours of basal-ganglion depth and 15 hours of midbrain depth. The minimum coma dose was 140 units; the maximum, 1,000 units; the average, 262 units. The total insulin units administered was 11,560. Social improvement resulted.

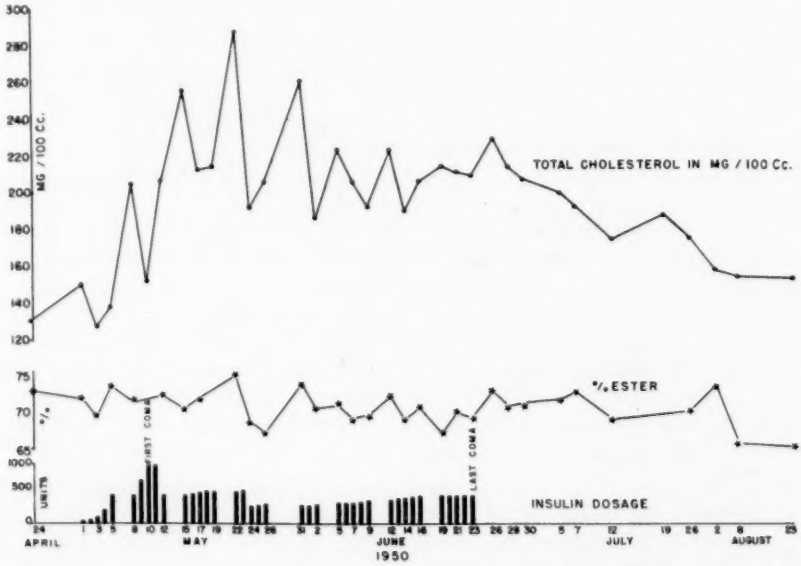

Chart 2.—A. V. D., with a diagnosis of schizophrenia, had 31 comas, 123 hours of insulin therapy, and 32 hours of unconsciousness, 5 hours being of midbrain depth and 27 hours of basal-ganglion depth. The minimum coma dose was 250 units; the maximum, 800 units; the average, 389 units. A total of 13,830 units of insulin was administered. Social improvement resulted.

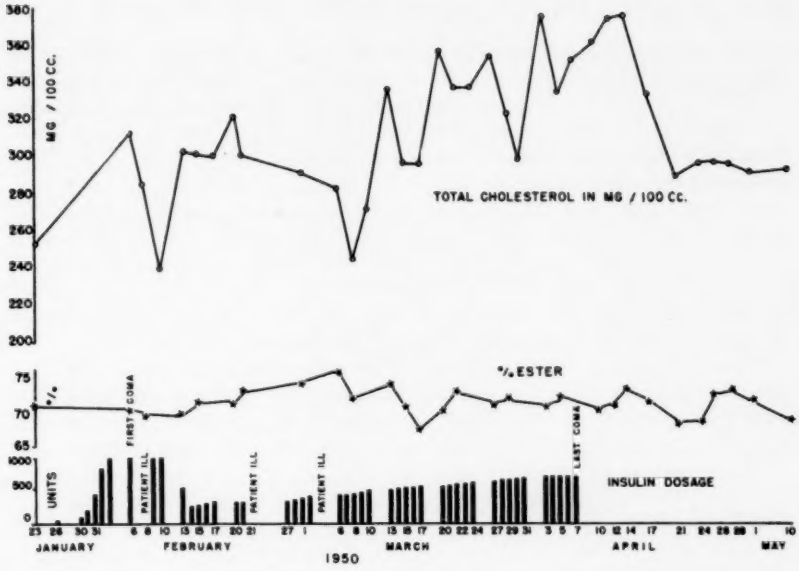

Chart 3.—J. W. H., with a diagnosis of schizophrenia, paranoid type, had 37 comas, 153 hours of insulin therapy, and 26½ hours of unconsciousness, with 24 hours of basal-ganglion depth and 2 hours of midbrain depth. The minimum coma dose was 250 units; the maximum, 1,000 units; the average, 541 units. The total units of insulin administered was 23,730. Administrative improvement resulted.

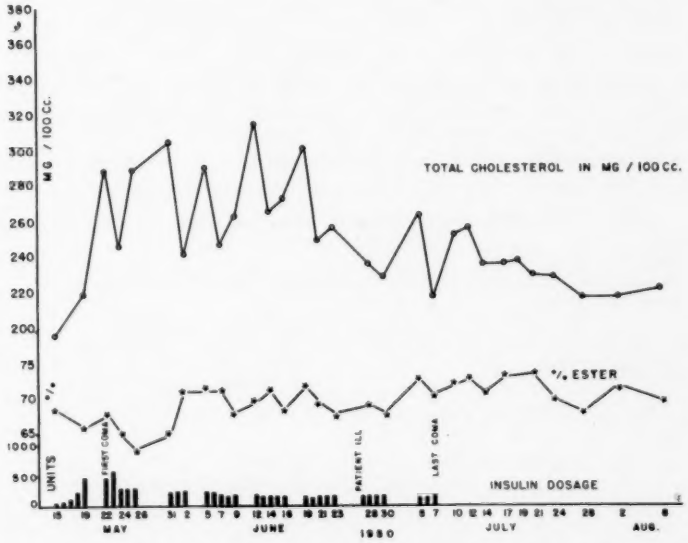

Chart 4.—R. J., with a diagnosis of schizophrenia, unclassified, had 30 comas, 108 hours of insulin therapy, and 44 hours of unconsciousness, with 37 hours of basal-ganglion depth and 7 hours of midbrain depth. The minimum coma dose was 120 units; the maximum, 500 units; the average, 183 units. The total units of insulin administered was 6,250 units. Social improvement resulted.

counts, which have been shown by Baird and Dixon [8] to drop 2½ to 3½ hours after the administration of insulin, with a return to morning levels by late afternoon or early evening. A few series of counts were run, with the Randolph [9] procedure for staining and counting eosinophiles. This drop was found to occur each time; therefore patients were routinely sampled twice daily, once at 9:30 a. m., for a morning level, and, again, at 11:45 a. m. to approximate the bottom of the decline. Frequently, the afternoon and evening return overshot the morning level, resulting in a developing eosinophilia with each successive coma and its concomitant drop in eosinophiles daily during the week of therapy. This increase in eosinophiles reached as high as 1,100 per cubic millimeter in patients that had preinsulin levels near 150 per cubic millimeter. The eosinophile response in these patients has been analyzed in more detail by Dr. Thomas Jones and is to be reported elsewhere.

The usual week-end pattern for eosinophiles was a gradual decline—not so rapid nor so great as the drop that occurred on days of insulin coma. The eosinophile pattern of decreases on week ends and increases during the week was not so consistent as the cholesterol pattern of increases on week ends and decreases with successive days of therapy.

It was also considered that with a sufficiently large number of cases it might be possible to correlate the characteristics of the cholesterol curve with the physiological and psychiatric response of the patient. For example, some of the curves (Charts 1 and 3) showed a continuously increasing peak from Monday to Monday; others (Chart 2) showed a maximum Monday peak about the third or fourth week of therapy, with a subsequent falling off. Others (Chart 4) maintained a nearly steady week-end response; that is, each Monday high was about the same or showed only a slight drop throughout the course of therapy. No conclusion from this observation can be considered until many more cases have been studied.

SUMMARY

A definite pattern of changes in blood cholesterol levels has been observed in schizophrenic patients during a course of insulin coma therapy. There was a definite and consistent increase on week ends after a series of five insulin comas, with concomitant decreases during the treatment periods. This pattern may possibly be related to the endocrine response of the patient to the therapy.

Dr. Joseph Crocket cooperated in obtaining serum specimens and made the psychiatric evaluations.

8. Baird, E. E., and Dixon, K. P.: Effects of Insulin on the Blood Picture, Am. J. Clin. Path. **18**:470-484, 1948.

9. Randolph, T. G.: Differentiation and Enumeration of Eosinophils in the Counting Chamber with a Glycol Stain: A Valuable Technique in Appraising ACTH Dosage, J. Lab. & Clin. Med. **34**:1696-1701, 1949.

ETIOLOGY AND TREATMENT OF URINARY LITHIASIS IN SEVERE POLIOMYELITIS

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AND
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MINNEAPOLIS

A CURSORY search of the urological literature has revealed only one title in recent years referring to the occurrence of urinary lithiasis in poliomyelitis.[1] Boyd [2] mentioned it in a discussion of lithiasis in bedridden patients, and there are probably other such references, since the relationship appears to be a fairly frequent one. It may be that the prolonged survival of patients with severe poliomyelitis is of such recent development that there has not been sufficient time for the situation to attract much attention.

It has long been known that diseases and disorders requiring prolonged immobilization in bed are frequently complicated by urinary lithiasis, particularly if there is extensive disease of bone (severe fractures, osteomyelitis) or paralysis. Factors which may lead to stone formation in such circumstances include (1) hypercalcinuria from disuse atrophy of the skeleton; (2) stasis in the dependent renal calices; (3) concentration of the urine from chronic dehydration; (4) alkalization of the urine (diet, alkaline medication, infection with urea-splitting bacteria); (5) deficiencies of vitamin A, and (6) presence of foreign bodies in the urinary tract. It seems likely that the first two factors are the important ones but that any of the others may appear at times as complications of the first two. Metabolic defects leading to cystinuria and xanthinuria and endocrine disorders, such as hyperparathyroidism, are unimportant here unless they were operative before the condition requiring immobilization, and so will not be discussed in this paper.

It is well known that decalcification of the skeleton follows prolonged immobilization in bed. Flocks,[3] Mayer and Mogenson,[4] and Cordonnier and Talbot,[5] among

From the Divisions of Urology and Neurology, University of Minnesota Medical School.

1. Brady, L., and Wilson, W. J.: Major Urological Surgery on Poliomyelitic Patients Confined to Respirators: Discussion on Etiology, Prophylaxis Against and Treatment of Calculi in Recumbent Patients, J. Urol. **60**:381, 1948.

2. Boyd, M. L.: Formation of Renal Calculi in Bedridden Patients, J. A. M. A. **116**:2245, 1941.

3. Flocks, R. H.: Preventive Treatment of Calcium Urolithiasis: Important Role of Early and Frequent Roentgenographic Examinations, J. Urol. **53**:427, 1945.

4. Mayer, J., and Mogenson, E.: On the Formation of Calculi in Urinary Tract of Patients with Osteo-Articular Tuberculosis, Acta chir. scandinav. **97**:259, 1948.

5. Cordonnier, J. J., and Talbot, B. S.: Effect of Ingestion of Sodium Acid Phosphate on Urinary Calcium in Recumbency, J. Urol. **60**:316, 1948.

others, have found the urinary calcium increased in many immobilized patients. Albright and Reifenstein [6] have emphasized that the normal stimuli to osteoblastic activity are stress and strain; immobilization decreases osteoblastic activity while resorption continues, so that osteoporosis develops. They have observed that the serum calcium remains normal if immobilization is gradual but is likely to rise sharply after sudden immobilization. Deitrick, Whedon, and associates [7] placed four young men in casts for five to six weeks; each subject lost from 9 to 24 gm. of calcium, or from 1 to 2% of his total calcium.

Joly [8] advanced several reasons for the precipitation of calcium salts in the calices and pelvis during prolonged recumbency and its attendant hypercalcinuria. First, all the calices on one side are dependent in lateral decubitus. Only in the prone position do all of the calices drain by gravity into the renal pelvis. Since no bedfast patient is ordinarily made to spend any appreciable time prone (a practical impossibility in the respirator), stagnation of urine in dependent calices obviously must occur. Actually, one may see the first evidence of lithiasis in the terminal cups of the calices, which may be outlined by fine sand. Joly also pointed out the futility of "flushing" the calices by the forcing of fluids. He calculated that a urine output of 1,500 cc. per day will cause an output of but 3 drops per calyx per minute. Since it is difficult to persuade most patients to maintain an output of 3,000 cc. per day, it is evident that no really effective flushing of the renal collecting system can be achieved in this manner. However, it seems reasonable to assume that, other things being equal, the forcing of fluid will at least discourage the precipitation of urinary salts by keeping them well diluted.

Joly [8] expressed the belief that hypercalcinuria led to precipitation in the renal urine of masses of crystalline or amorphous salts of calcium. Being heavier than urine, they sink into the dependent calices, and lithiasis is under way. It was suggested by Schade,[9] Lichtwitz,[10] and others that, since normal urine is ordinarily a supersaturated solution, the crystalloids must be kept from precipitating by those colloids which are normally present in the urine, and which can exert a protective action upon supersaturated solutions of crystalloids in vitro. Unfortunately, it has been impossible to take advantage of this action of the colloids clinically, although Butt [11] has recently suggested that hyaluronidase may be used for this purpose. Flocks [8] believed that the most important factors in the actual initiation of lithiasis are the concentration of calcium and phosphorus in the urine and the urinary pH.

6. Albright, F., and Reifenstein, E. C., Jr.: Parathyroid Glands and Metabolic Bone Disease; Selected Studies, Baltimore, Williams & Wilkins Company, 1948, pp. 135, 145.

7. Deitrick, J. E.; Whedon, G. D.; Shorr, E., and Barr, D. P.: Effects of Bed Rest and Immobilization upon Various Physiological and Chemical Functions of Normal Men, Conference on Metabolic Aspects of Convalescence, Including Bone and Wound Healing, Transactions of the Ninth Meeting of the Josiah Macy Jr., Foundation, New York, 1945, pp. 62-81; cited by Albright and Reifenstein.[6]

8. Joly, J. S.: Stone and Calculous Disease of the Urinary Organs, St. Louis, C. V. Mosby Company, 1929, pp. 30-65.

9. Schade, H. B.: Beitrage zur Konkrementbildung, München. med. Wchnschr. **56**:77, 1909.

10. Lichtwitz, L.: Die Bildung der Harnsediment und Harnsteine, Ztschr. Urol. **7**:810, 1913.

11. Butt, A. J.: Role of Protective Urinary Colloids in Prevention of Urinary Lithiasis, J. Urol. **67**:450, 1952.

The predisposition to lithiasis is greatly increased if stagnation of urine in the dependent calices is aggravated by hydronephrosis secondary to paralysis of the bladder, such as accompanies paraplegia regularly and poliomyelitis occasionally. Toomey [12] attributed it in poliomyelitis to an associated peripheral neuritis. Bühler [13] found urinary calculi in 11 of 32 patients with fractured spines. Prather [14] followed 60 paraplegic patients for 15 months; 30% of those with complete and 20% of those with incomplete transection of the cord had stones develop during this period.

The importance of a protracted high concentration of the urine due to sweating and to an inadequate intake of fluid is difficult to assess but, since calculi consist of salts normally present in the urine, it is logical to suppose that it may be an important factor if other conditions which favor lithiasis are operative. Its potential importance is suggested by the observations of Pierce and Bloom [15] and of Rose [16] that American and Australian troops, freshly arrived in desert areas, were likely to pass urine so concentrated as to be almost syrupy. This was frequently followed by renal colic and hematuria, owing to the passage of agglomerations of crystals, or even of true stones. Davalos,[17] on the other hand, found that lithiasis is extremely rare in southern Ecuador, where the climate is exceedingly hot, but wet.

Experimental evidence of the importance of a high output of urine in the management of lithiasis has been adduced by Grove, Vermeulen, Goetz, and Ragins.[18] They produced vesical calculi by introducing bits of zinc into the bladders of rats. With a standard intake of food and fluid, urinary salts were deposited upon the zinc at a fairly constant rate. They could prevent this deposition of salts upon new foreign bodies, or dissolve a good part of it from old ones, with the aid of diuresis induced by the substitution of a 10% glucose solution for the drinking water. The presence of urea-splitting organisms prevented this effect.

It has been suggested that the prolonged ingestion of a diet with an alkaline ash, or of alkaline salts used in the treatment of peptic ulcer, could lead to the formation of stones through the precipitation of the phosphates and carbonates of the alkaline earths in the alkaline urine. Kretschmer and Brown [19] reviewed the records of a considerable number of patients who had been on Sippy's regimen for long periods.

12. Toomey, J. A.: Intestine and Urinary Bladder in Poliomyelitis, Am. J. Dis. Child. **45**:1211, 1933.

13. Bühler, F.: Beiträge zur Frage der Urolithiasis besonders in Verbindung mit Leukämie und Rückenmarksverletzungen, Ztschr. urol. Chir. **37**:406, 1933.

14. Prather, G. C.: Spinal Cord Injuries: Calculi of the Urinary Tract, J. Urol. **57**:1097, 1947.

15. Pierce, L. W., and Bloom, B.: Observations on Urolithiasis Among American Troops in a Desert Area, J. Urol. **54**:466, 1945.

16. Rose, T. F.: Urinary Colic Due to Crystalluria and Calculi in Hot, Humid Climates, M. J. Australia **1**:558, 1945.

17. Davalos, A.: Rarity of Stones in the Urinary Tract in the Wet Tropics, J. Urol. **54**:182, 1945.

18. Grove, W. J.; Vermeulen, C. W.; Goetz, R., and Ragins, H. D.: Experimental Urolithiasis: Influence of Urine Volume upon Calculi Experimentally Produced upon Foreign Bodies, J. Urol. **64**:549, 1950.

19. Kretschmer, H. L., and Brown, R. C.: Do Alkalies Used in Treatment of Peptic Ulcer Cause Kidney Stones? J. A. M. A. **113**:1471, 1939.

The incidence of urinary stones in this group was no higher than in an untreated group of patients of similar size and age distribution.

The alkalization of the urine which results from infection of the urinary tract with urea-splitting bacteria, particularly the Proteus vulgaris, is quite another matter. The resultant alkalinity cannot be corrected in the presence of stasis or foreign bodies in the urinary tract and so leads to the precipitation described above. Such infections are greatly to be feared whenever an inlying catheter has to be used, because the organisms are frequently resident in the normal bowel. Creevy [20] found that they could often be cultured from the used bed sheets of hospital patients, even in the absence of gross soiling by feces. It is fairly obvious that the Proteus may contaminate a catheter, either directly, when the latter comes in contact with the anus, or indirectly, by way of contaminated bedclothes. Brown [21] recognized this organism as a cause of stone formation in 1901. Hager and Magath [22] produced encrusting cystitis with it in the rabbit; Suby and Suby [23] observed renal lithiasis in the rabbit after its intravenous injection. Of a series of 2,537 cases of urinary stones collected from the literature in 1941, Creevy [20] found that lithiasis was associated with bacteriuria in 65%. P. vulgaris was found in 11% of these, or in 7% of the whole group. Joly [8] and Chute [24] commented upon the frequency with which this organism appears to be responsible for recurrence of renal calculi after operation.

Other organisms may split urea at times and have the same effect as P. vulgaris. Some strains of Pseudomonas aeruginosa, Micrococcus pyogenes var. aureus, Escherichia coli, and Hemophilus influenzae have been incriminated. Bacteria may contribute to the formation of stones in other ways than by splitting urea. Scholl [25] reported two instances in which stones appeared to be composed almost entirely of the bodies of dead bacteria, and he collected eight similar cases from the literature. Hellström [26] has reported frequently upon the role of staphylococci in urinary lithiasis. Eisenstaedt [27] found bacterial nuclei in 29 stones, and such formations have been described by many others. Rosenow and Meisser [28] implanted pleomorphic streptococci recovered from dental cavities in patients with renal calculi into artificial cavities in the teeth of dogs and thereafter observed stones in the kidneys

20. Creevy, C. D.: Nephrolithiasis Due to Infection with the Bacillus Proteus, Surgery **10**:971, 1941.

21. Brown, T. R.: On the Relation Between the Variety of Micro-Organisms and the Composition of Stone in Calculous Pyelonephritis, J. A. M. A. **36**:1395, 1901.

22. Hager, B. H., and Magath, T. B.: Four Cases of Urinary Calculi from Which Proteus Ammoniae Was Isolated, M. Clin. North America **10**:693, 1926; Formation of Vesical Calculi, J. A. M. A. **90**:266, 1928.

23. Suby, H. I., and Suby, R. M.: Experimental Production of Kidney Stones with Urea-Splitting Organisms, J. Urol. **57**:995, 1947.

24. Chute, R.: Significance of Urea-Splitting Bacteria in the Formation of Urinary Calculi, New England J. Med. **219**:1030, 1938.

25. Scholl, A. J.: Bacterial Concretions in Kidney Pelvis, with Report of Two Personal Cases, Surg., Gynec. & Obst. **55**:360, 1932.

26. Hellström, J.: Staphylokokkurie und Nierensteine, Ztschr. urol. Chir. **30**:173, 1930.

27. Eisenstaedt, J. S.: Certain Tangible Factors in the Etiology of Urinary Calculus, Surg., Gynec. & Obst. **53**:730, 1931.

28. Rosenow, E. C., and Meisser, J. G.: Production of Urinary Calculi by Devitalization and Infection of Teeth in Dogs with Streptococci from Cases of Nephrolithiasis, Arch. Int. Med. **31**:807, 1923.

of the dogs. Hewitt [29] found that a wide variety of bacteria, if grown upon a medium containing insoluble salts of calcium, would produce "bodies" of calcium carbonate upon the surface of the medium. He speculated whether these could occur in infected urine and serve as the nuclei for stones.

The role of deficiencies of vitamin A in the production of urinary stones in man has been the subject of much speculation ever since Osborne and Mendel [30] in 1917 showed such a deficiency to be capable of causing stones in the rat. This observation was verified by McCarrison,[31] by Higgins,[32] and by others, but no vitamin-A deficiency has been shown conclusively to be an etiological agent in man under ordinary circumstances in this country. However, it is wise to bear in mind the possibility in dealing with patients with debilitating illnesses. Hypervitaminosis D has been reported as a causative factor in the production of renal calculi.

While it is generally known that foreign bodies in the urinary tract invariably become encrusted with urinary salts if they remain long enough in contact with urine, and that the rate of deposition is greatly increased by infections with urea-splitting organisms, this factor must be considered in the present discussion only in so far as catheters left inlying for too long a time without a change may become coated with phosphates and carbonates, especially in the presence of urea-splitting bacteria. If fragments of this coating break off in the bladder, they may serve as nuclei for stones.

REPORT OF CASES

CASE 1.—A. S., a 39-year-old farmer, was hospitalized in October, 1948, with acute bulbospinal poliomyelitis. He had not only tetraplegia but also severe vagal and respiratory paralysis and required a tracheotomy and respirator. He was critically ill for six weeks, pneumonia, atelectasis, and severe furunculosis complicating the course. In May, 1949, the tracheotomy tube was removed, and the patient tolerated 30 minutes out of the respirator. By August, 1949, he tolerated eight hours out of the respirator, and function of scattered arm muscles had been partially restored. Since then there has been no remarkable improvement, and the lower extremities have remained completely flaccid.

Prior to his illness, the patient's general health had been excellent, and he had no genitourinary complaints. He had urinary retention for 24 hours before admission to the hospital, and an inlying catheter was necessary for the following 19 days. Urinalysis on admission and weekly urinalyses through August, 1949, showed only occasional minimal pyuria and albuminuria, except for two episodes of 2+ pyuria and 1+ albuminuria in December, 1948.

In September, 1949, occasional erythrocytes and leucocytes were noted on urinalyses, and the patient had dull, aching pain in the right upper quadrant and the lumbar area. X-ray examination revealed multiple, small renal calculi on the right (Fig. 1). The patient received an acid-ash diet, a high fluid intake, and nitrohydrochloric acid in October, 1949, but refused to continue this therapy after three weeks; hence this program was discontinued. In December, 1949, and January, 1950, the patient had episodes of severe epigastric pain, nausea, dysuria, and increased urinary frequency. There were marked costovertebral tenderness on the left and a spiking fever. On one occasion there were severe dysuria and hematuria, but no calculi could be found in the specimen of urine. Urinalysis showed moderate pyuria, and cultures of urine yielded no growth. The fever and pain subsided after three days of aureomycin therapy. An

29. Hewitt, H. B.: Bacterial "Calculi," J. Path. & Bact. **59**:657, 1947.

30. Osborne, T. B., and Mendel, L. B.: Incidence of Phosphatic Urinary Calculi in Rats Fed on Experimental Rations, J. A. M. A. **69**:32, 1917.

31. McCarrison, R.: Experimental Production of Stone in the Bladder, Brit. M. J. **1**:717, 1927.

32. Higgins, C. C.: Production and Solution of Urinary Calculi: Experimental and Clinical Studies, J. A. M. A. **104**:1296, 1935.

intravenous urogram showed multiple renal calculi on the right and a small calculus at the left ureteropelvic junction (Fig. 1). Cystoscopic examination revealed a normal bladder except for Grade-1 trabeculation and residual urine of 10 cc. The left ureter was catheterized with ease.

Since January, 1950, the patient has had no further episodes of renal colic, although occasional urinalyses have shown mild hematuria and pyuria. Repeated roentgenograms have shown no change in the renal calculi. The patient was maintained on an acid-ash diet and basic aluminum carbonate gel (basaljel®) until his discharge from the hospital, in July, 1950.

Comment.—This patient spent over 95% of the first eight months of his illness in the "iron-lung" type of respirator and could be moved only partially to either side because the close approximation of the respirator collar to the tracheotomy

Fig. 1 (Case 1).—Intravenous urogram showing multiple right renal calculi and a small calculus at the left ureteropelvic junction.

tube limited any neck movements. During this time he also had difficulty with heavy mucoid secretions in his trachea, and fluids often had to be restricted to control this problem, as well as to prevent pulmonary edema. The average daily fluid intake for the first six months was less than 2,000 cc. Physical therapy was also limited because of the difficulty in working with a respirator patient, and particularly because of his prolonged critical state. An inlying catheter also was used almost three weeks at the beginning of his illness. Thus, there were multiple factors evident which may have produced the nephrolithiasis.

Case 2.—D. M., a 28-year-old housewife, was hospitalized in September, 1950, with acute bulbospinal poliomyelitis. Respirator care and tracheotomy were necessary, and the patient had

tetraplegia. During her acute illness she had episodes of diarrhea and tarry stools and required transfusions. The tracheotomy tube was removed in the last week of November; at that time the patient tolerated 1½ minutes out of the respirator. Thereafter, she gradually increased her time outside, so that by December, 1951, she tolerated four hours at a time. Her only return of muscle function was in scattered muscles of the lower arms and hands.

The patient's past general health had been excellent. On admission she had acute urinary retention, and an inlying catheter was necessary for one month. Repeated episodes of 2+ to 3+ pyuria were noted during the entire period of hospitalization (September, 1950 to November, 1951).

In March, 1951, the patient had an episode of severe bilateral lumbar and upper-quadrant pain, abdominal distention, nausea, and vomiting. Urinalysis showed heavy pyuria and mild

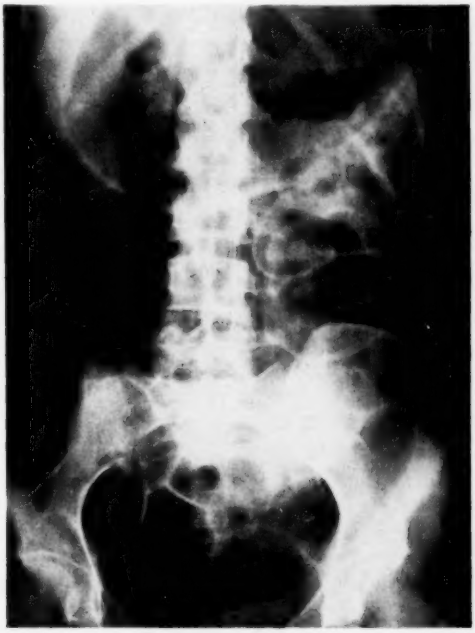

Fig. 2 (Case 2).—Roentgenogram showing definite ileus and clusters of calculi in the right renal pelvis.

hematuria and albuminuria. A culture of the urine showed P. vulgaris. A roentgenogram revealed definite ileus and clusters of calculi in the right renal pelvis, as well as in the lower end of the left ureter (Fig. 2). Cytoscopic examination disclosed poor indigo-carmine excretion from the left ureter, and a catheter was left in this ureter for five days. A combination of streptomycin, chloramphenicol, and aureomycin was used, and the patient was put on a regimen of basaljel* and an acid-ash diet. She then felt well, and urinalyses and cultures of the urine showed nothing abnormal until June, 1951, when she had a similar episode of pain, fever, and abdominal distention. Culture of the urine showed P. vulgaris and Esch. coli, and a roentgenogram showed a ureteral calculus on the right. The stone had disappeared when a second roentgenogram was taken, two days later. Sulfisoxazole ("gantrisin") and chloramphenicol were used, and the patient recovered in one week.

The patient has since remained well, although showing occasional pyuria and mild hematuria, and x-ray examination in October, 1951, showed a definite decrease in the mass of renal calculi. General demineralization of bone was noted in all roentgenograms.

Comment.—The same problems were encountered in this case as in Case 1 with reference to the factors of relatively constant respirator care for several months, fluid restriction, limited physical therapy, and the use of an inlying catheter for one month. Recurrent infection with P. vulgaris undoubtedly played an important role. The episodes of pyelonephritis and the passage of calculi have produced further alterations in the urinary tract conducive to future infections. The patient's general health and ability to maintain herself out of the respirator have been impaired by the repeated urinary-tract complications, and the over-all prognosis for life expectancy is guarded because of the influence of these factors.

PREVENTION OF STONES IN PROTRACTED RECUMBENCY

It is evident from the foregoing report that any patient who has to be immobilized in bed for a long period, particularly if he has extensive disease of bone or paralysis, must be handled with great care if lithiasis of the urinary organs is to be avoided.

Osteoporosis and the consequent hypercalcinuria may be minimized by the diligent employment of active and passive exercise, since, as Albright and Reifenstein [6] have pointed out, stress and strain stimulate osteoblastic activity, thus preventing the excessive excretion of calcium. In a youth of 14, who was in a cast because of a fracture through a cyst of the femur, these authors apparently caused the serum calcium to fall from a level of 14 mg., which it had attained during immobilization, to 11.3 mg. per 100 cc. simply by getting him out of bed for exercise. It is difficult or impossible in most circumstances to employ enough passive and active exercise for this purpose in paraplegic patients and in victims of bulbar poliomyelitis, both because paralyzed muscles cannot be exercised actively and because of lack of a sufficient number of trained personnel. However, passive exercise should be used just as much as circumstances permit.

Stasis in dependent calices may, as stated by Joly,[8] be counteracted effectively in the patient who cannot sit or stand only by requiring him to spend stipulated periods at regular intervals in the prone position. This measure, too, is probably impractical for the patient confined to the respirator; even those who are able to spend part of the time out of the respirator may be unable to breathe while prone because of the necessity for lifting the chest with the weakened respiratory muscles. One wonders whether some apparatus could not be devised to permit these patients to breathe while prone, since the nephrolithiasis which often afflicts the "respirator patient" is likely finally to cause his death, despite the expenditure of tremendous amounts of thought, energy, time, and money in keeping him alive during the acute phase of the disease. The current use of the chest respirator and tilting bed may provide more freedom of movement for these patients and enable physical therapy to be more adequately administered. Although these apparatuses generally are not so effective as the tank type of respirator in the critically ill patient with severe respiratory paralysis, they should be used during convalescence as soon as the patient can tolerate them.

Concentration of the urine is readily prevented by giving the patient enough fluid to insure a urine output of 2,000 to 2,500 cc. per day. Even this may be a

problem with the seriously ill patient, especially if he is confined to the respirator or is presenting evidence of pulmonary edema or excessive mucous secretion in the throat. It is, however, usually a question of remembering to see that the necessary fluid is given, whether by mouth, by nasal tube, or by intravenous drip. The value of the high fluid intake lies in discouraging the precipitation of calcium salts by keeping them in dilute solution.

The reaction of the urine is best controlled, in the absence of infection with urea-splitting bacteria, by giving an acid-ash diet. This means that citrus fruits and large quantities of leafy vegetables must be avoided, the necessary vitamins being given as such. Acids and acid salts are not to be used because they may increase the absorption of calcium from the bowel, and consequently its excretion in the urine.[33] The same may be said of the ingestion of large amounts of vitamin D; milk is so rich in calcium that its use should be restricted. If infection with a urea-splitting organism occurs, the urine cannot be acidified in the presence of stasis or of foreign bodies (catheters), even by sending the patient into acidosis, without first eliminating the bacteria (see below).

In view of the uncertain role of deficiencies of vitamin A in the production of urinary stones, it is wise to employ an adequate intake of that vitamin. A daily amount of 10,000 I. U. should be more than enough.

Infection of the urinary tract by P. vulgaris or other urea-splitting organism is of such serious significance in these patients that it should be watched for by means of weekly cultures of the urine if an inlying catheter or frequent intermittent catheterization has to be employed. A real effort should be made to see to it that all catheters, tubing, and glassware used in this connection are carefully cleansed of all traces of urinary salts and sterilized effectively. Chute [24] has emphasized that the urea-splitting organisms resist sterilization if protected by encrustations of this type. Cheap tubing should be used to connect the inlying catheter to receiving bottles for the urine and discarded when it becomes encrusted. A closed system of irrigation with a two-way inlying catheter is preferred to open irrigation with an ordinary one, since it reduces the danger of contamination of the catheter during open irrigation by inexperienced or careless personnel. Antibiotics should be used routinely in small doses whenever an inlying catheter has to be used. They will rarely prevent infection entirely, but may serve to minimize it. The drug should be changed from time to time to discourage the development of bacterial resistance.

Once P. vulgaris is found in the urine, basaljel[®] (30 cc. four times daily) should be given, as recommended by Shorr [34] for recurrent nephrolithiasis, in order to minimize the excretion of phosphorus in the urine. There is as yet no direct evidence that this measure is helpful in the situation under discussion, but Shorr's results in circumstances just as difficult have been such as to justify its employment. Since its use will reduce the urinary concentration of one of the most important constituents of the stones which occur both in prolonged immobilization and in infections with the urea-splitting organisms, it might be well to administer it even in the absence of infection.

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33. Creevy.[20] Albright and Reifenstein.[6]

34. Shorr, E.: Possible Usefulness of Estrogens and Aluminum Hydroxide Gels in the Management of Renal Stones, J. Urol. **53**:507, 1945. Shorr, E., and Carter, A. C.: Aluminum Gels in the Management of Renal Phosphatic Calculi, J. A. M. A. **144**:1549, 1950.

P. vulgaris is exceedingly difficult to eliminate from the urine when there is any appreciable stasis or when a catheter or other foreign body is present. It is probably better to withhold specific antibiotic therapy directed at this organism until such conditions can be corrected, since premature treatment will probably succeed merely in making the organisms resistant to the drugs used. When stasis has been eliminated or minimized and the catheter is no longer needed, sterilization of the urine is most likely to follow the use of chloramphenicol, 0.5 gm., and sulfisoxazole, 2.0 gm., four times daily for a week, followed during the second week by one-half this dose, and during the third week by one-fourth the original dose. In our hands, this regimen has been successful in about two-thirds of a small series under fairly unfavorable circumstances. Until the advent of this combination, our only success in eradicating this organism had followed the use of large doses of penicillin and streptomycin, and this medication was effective only rarely.

The other urea-splitting organisms have to be treated on a catch-as-catch-can basis, by trying different antibiotics in various combinations and sequences.

SUMMARY AND CONCLUSIONS

The factors which predispose to urinary lithiasis in patients with poliomyelitis are undoubtedly the same as those which exist in any disease which results in prolonged immobilization in recumbency (traumatic paraplegia, extensive disease of bone).

These factors include osteoporosis from disuse, with resultant hypercalcinuria; stasis in the dependent calices of the kidneys; overconcentration of the urine from inadequate intake of fluid; prolonged alkalization of the urine; deficiencies of vitamin A (?); the presence of foreign bodies in the urinary tract, and infections of the urinary tract with the bacteria which split urea.

Two cases of poliomyelitis complicated by nephrolithiasis are presented to point up the difficulties encountered in controlling these factors.

Measures useful in combating the tendency to lithiasis include the maximum possible use of passive and active exercise to prevent or to minimize osteoporosis; frequent changes in position to discourage stasis in dependent calices, although this measure cannot really be effective unless the prone position can be employed; a high fluid intake; an acid-ash diet with vitamin supplements (except for vitamin D) and a low intake of milk; aseptic handling of catheters and their accessories; the judicious use of antibiotics, and the employment of basic aluminum carbonate gel (basaljel®) to reduce the phosphorus content of the urine.

EFFECTS OF HYPNOTIC SUGGESTION ON PAIN PERCEPTION AND GALVANIC SKIN RESPONSE

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RECENTLY there has been a revival of interest in clinical applications of hypnosis. At the same time, renewed use of anesthesia induced by hypnotic suggestion has been seen, particularly in the fields of obstetrics and dentistry. Hypnotic anesthesia is especially interesting because of the conflicting and challenging nature of reports in the literature. While there has been considerable progress in psychotherapeutic employment of hypnosis,[1] little has been added to our understanding of its physiological aspects. The literature on the physiology of hypnosis has been recently reviewed by Gorton,[2] whose article serves to emphasize the necessity for considerable controlled experimentation if many disputed points are to be clarified.

In 1845 Esdaile[3] performed many minor and major operations, including amputations, using hypnotic anesthesia. He claimed that his patients offered no complaint of pain, lay quietly during the surgical procedures, and failed to show changes in pulse or respiration rate or in pupillary dilation, usually considered objective physiological signs of pain. For a time hypnotic anesthesia was rather widely employed by surgeons, and Bramwell's review of the topic covers it in a

These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and Cornell University Medical College.

Dr. Augusta S. Alba aided in preparation of the equipment, and Dr. Charles Knehr and Mrs. Kathryn L. West assisted in statistical analysis of the data.

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Read at the combined meetings of the New York Neurological Society, the Philadelphia Neurological Society, and the New York Academy of Medicine, and the Section of Neurology and Psychiatry, April 27, 1951. An abstract of this paper, with discussion, was published in the May 1952 issue of the ARCHIVES, page 694.

1. Brenman, M., and Gill, M. M.: Hypnotherapy: A Survey of the Literature, with Appended Case Reports and an Experimental Study, Menninger Foundation Monograph No. 5, New York, Josiah Macy Jr. Foundation, 1944. Wolberg, L.: Medical Hypnosis, New York, Grune & Stratton, Inc., 1948.

2. Gorton, B. E.: The Physiology of Hypnosis, Psychiatic Quart. **28**:457, 1949.

3. Esdaile, J.: Mesmerism in India and Its Practical Application in Surgery and Medicine, London, Longman, Brown, Green & Longman, 1846.

general way up to 1930.[4] An interesting discussion of claimed clinical advantages of hypnotic over chemical anesthesia was given by Hollander.[5]

Physiological studies of hypnotic anesthesia have incorporated measurements of the galvanic skin response, heart rate, facial flinch, respiration, and vasomotor reactions. No quantitative study of pain perception in hypnosis was reported prior to the development of the Hardy-Wolff-Goodell technique for administration of painful stimuli in the form of known amounts of radiant heat.[6] This technique permits the correlation of subjective impressions of pain threshold and pain intensity, in terms of the dol scale,[7] with objective measurement of the stimuli, in terms of millicalories per second per square centimeter. Using this technique, Wolff and Goodell reported in 1943 [8] that in one subject, placed in "shallow hypnosis" by Diethelm, suggestions of anesthesia raised the pain threshold 40%. These authors stressed the importance of considering separately pain sensation and reactions to pain when one is analyzing the effect of a procedure upon the subject. Thus, to study the influence of hypnotic suggestion on pain sensation, they made measurements of pain threshold and pain intensity on subjects in the unhypnotized and then in the hypnotized state. The galvanic skin response was selected as a convenient index of the reaction of the subject to pain.

According to Landis,[9] the galvanic skin response consists of (1) decreased apparent resistance of the skin, due to physiological activity under the control of the autonomic nervous system, following sensory or ideational stimulation, and (2) increase in the apparent electromotive force of the skin. These effects are usually fused into a single response, which can be recorded by a photokymograph. The record is a wave-like curve, having a latent period of 3 to 5 seconds (or less) and a duration of 3 to 15 seconds. Furer and Hardy [10] have recently studied the galvanic skin response to pain stimuli of increasing intensity. They concluded that the galvanic skin response is a measure of the "threat content" of a painful stimulus. In the light of their findings, it was decided to utilize the same technique in an investigation of hypnotic anesthesia.

REVIEW OF LITERATURE

A number of articles have appeared regarding the relation of the galvanic skin response to painful and other stimuli, but there is disagreement on the question of

4. Bramwell, J. M.: Hypnotism: Its History, Practice and Theory, Ed. 4, Philadelphia, J. B. Lippincott Company, 1930.

5. Hollander, B.: Hypnosis and Anesthesia, Proc. Roy. Soc. Med. **25**:598, 1932.

6. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain: A New Method for Measuring Pain Threshold; Observations on Spatial Summation of Pain, J. Clin. Invest. **19**:649, 1940.

7. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain Discrimination of Differences in Intensity of a Pain Stimulus as a Basis of a Scale of Pain Intensity, J. Clin. Invest. **26**:1152, 1947.

8. Wolff, H. G., and Goodell, H.: The Relation of Attitude and Suggestion to the Perception of and Reaction to Pain, A. Research Nerv. & Ment. Dis., Proc. **23**:434, 1943.

9. Landis, C.: Electrical Phenomena of the Skin (Galvanic Skin Response), Psychol. Bull. **29**:10, 693, 1932.

10. Furer, M., and Hardy, J. D.: The Reaction to Pain as Determined by the Galvanic Skin Response, A. Res. Nerv. & Ment. Dis., Proc. (1949) **29**:72, 1950.

whether hypnotic anesthesia alters the reaction. Moravcsik,[11] in one case, and Georgi,[12] in three cases, found that stimulation of hypnotically anesthetized areas evoked no galvanic skin response. Peiper,[13] Prideaux,[14] and Prince and Peterson [15] reported opposing observations. In hysterical anesthesia, often thought to involve the same mechanism as hypnotic anesthesia, Veraguth [16] and Prideaux [14] found that stimulation of anesthetic areas gave normal galvanic skin responses; Gregor [17] obtained variable results. In a study of two hysterical patients, Levine [18] noted that a galvanic skin response was present after stimulation of cutaneous areas of both hypnotic and hysterical anesthesia. He also noted that hypnotically induced hallucinations of a needle prick produced a galvanic skin response. The presence of this reflex in the differentiation of hysterical anesthesia and malingering from anesthesias of organic origin has been described by Winn,[19] Golla,[20] Myasischev,[21] Sears and Cohen,[22] and Redlich.[23] In none of these studies was a systematic attempt made to measure the degree of change of skin resistance under different conditions. Such measurements were made by Sears [24] in a study of seven male subjects who were capable of deep trance, with complete analgesia and posthypnotic amnesia. Measurements revealed that the galvanic skin response, while present, was on the average decreased by 20% after stimulation of the anesthetized limb as compared with stimulation of the control limb. Sears also found that hypnotic anesthesia greatly reduced the variability in the pulse rate and practically eliminated the facial flinch and respiratory reactions to pain. Separate, unhypnotized controls indicated that voluntary inhibition of reactions to pain did not present a picture "even remotely resembling" the reactions (or lack of reaction) of subjects under hypnotic anesthesia. A subsequent study by Dynes [25] in general confirmed Sears's results regarding

11. Moravcsik, E. E.: Experimente über das psychogalvanische Reflexphänomen, Jahrb. Psychiat. u. Neurol. **18**:186, 1912.

12. Georgi, F.: Beiträge zur Kenntnis des psycho-galvanischen Phänomens, Arch. Psychiat. **62**:571, 1921.

13. Peiper, A.: Untersuchungen über den galvanischen Hautreflex (psychogalvanischen Reflex) im Kindesalter, Jahrb. Kinderh. **107**:139, 1924.

14. Prideaux, E.: The Psychogalvanic Reflex, Brain **43**:50, 1920.

15. Prince, M., and Peterson, F.: Experiments in Psychogalvanic Reaction from Co-Conscious (Subconscious) Ideas in Multiple Personality, J. Abnorm. Psychol. **3**:114, 1908.

16. Veraguth, O.: Das psychogalvanische Reflex Phänomen, Berlin, S. Karger, 1909.

17. Gregor, A.: Beiträge zur Kenntnis des psychogalvanischen Phänomens, Ztschr. Neurol. u. Psychiat. **8**:393, 1912.

18. Levine, M.: Psychogalvanic Reaction to Painful Stimuli in Hypnotic and Hysterical Anesthesia, Bull. Johns Hopkins Hosp. **46**:331, 1930.

19. Winn, R. C.: The Psychogalvanometer in Practice, Australia J. Psychol. & Phil. **7**: 1929.

20. Golla, F. L.: The Objective Study of Neurosis, Lancet **2**:115, 1921.

21. Myasischev, L.: Experimental Evidence on the Problem of Objective Indices in Sensory Disorders, Nov. refl. fiziol. nerv. sist. **3**:458, 1929; Psychol. Abstr. **4**:4349, 1930.

22. Sears, R. R., and Cohen, L. H.: Hysterical Anesthesia, Analgesia and Astereognosis, Arch. Neurol. & Psychiat. **29**:260, 1933.

23. Redlich, F. C.: Organic and Hysterical Anesthesia: A Method of Differential Diagnosis with the Aid of the Galvanic Skin Response, Am. J. Psychiat. **102**:318, 1945.

24. Sears, R. R.: Experimental Study of Hypnotic Anesthesia, J. Exper. Psychol. **15**:1, 1932.

25. Dynes, J. B.: Experimental Study Hypnotic Anesthesia, J. Abnorm. & Social Psychol. **27**:79, 1932.

cardiac and respiratory changes, but he observed the galvanic skin response to be "little influenced," showing "a slight decrease as compared with the normal," in seven subjects under hypnotic anesthesia in deep trance. Brown and Vogel [26] studied three subjects in deep hypnosis with the Darrow Photopolygraph. In contradiction to the results of Sears and of Dynes, they concluded that quantitative changes in physiological reactions to painful stimuli were not reliable indicators of painful experience, and that suggested analgesia in the hypnotic state did not abolish physiological reactions to sensory stimuli. Although they were of the opinion that imagination in the unhypnotized state might be as effective as hypnotic suggestion in influencing physiological reactions to pain, they found that hypersensitivity suggested during hypnosis could greatly increase these reactions. Doupe, Miller, and Keller [27] studied vasomotor reactions to pain and drew attention to the fact that reinforcement of repeated suggestions of anesthesia during the course of the experiment made for a decrease of vasomotor reactions to pain under hypnosis. They made rough distinctions between "moderate" and "severe" painful stimuli by pinprick, finding, paradoxically, that hypnotic anesthesia was more effective in reducing reactions to "severe" pain than to "moderate" pain.

The excellent reviews by Landis [9] and McCleary [28] contain the most recent survey of the literature on the galvanic skin response.

The present experiment differs generally from those reviewed above in the following respects:

1. The subjects were studied in various stages of hypnosis.

2. Quantitatively determined noxious stimuli were used instead of pinching or pinprick.

3. Changes in pain threshold were measured.

4. Quantitative estimates of pain intensity were made by the subject in the hypnotized and the unhypnotized state.

5. Changes in ability to discriminate between pains of differing intensity were noted.

6. Quantitative records of galvanic skin responses in the control and in the hypnotized state were utilized.

METHODS AND MATERIAL

Seven normal subjects, between the ages of 22 and 27, were used in this study; four were women and three were men. The experimental situation is diagrammed in Figure 1. The experiments were conducted in a room of constant temperature, the temperature being maintained at a comfortable level throughout each experimental session. The subject was placed in a supine position on a cot, which lay on top of a sturdy laboratory table. The dorsum of the left hand and forearm was blackened with India ink, and the height of the aperture of the dolorimeter was adjusted so that the skin surface could be placed against it comfortably. Electrodes were placed on the right hand for the measurement of skin resistances. The same two observers were present at each session.

26. Brown, R. R., and Vogel, V. H.: Psychophysiological Reactions Following Painful Stimuli Under Hypnotic Analgesia Contrasted with Gas Anesthesia and Novocain Block, J. Appl. Psychol. **22**:408, 1938.

27. Doupe, J.; Miller, W. R., and Keller, W. K.: Vasomotor Reactions in the Hypnotic State, J. Neurol. & Psychiat. **2**:97, 1939.

28. McCleary, R. A.: The Nature of the Galvanic Skin Response, Psychol. Bull. **47**:2, 97, 1950.

Quantitated noxious stimuli were administered according to the technique of Furer and Hardy.[10] The first measurement obtained at each session was the pain threshold, which was expressed in millicalories (mcal.) per second per square centimeter for a three-second exposure. From this value, stimuli evoking threshold pain, and pain of 2-, 4-, 6-, and 7-dol intensity were calculated on the basis of the formula used by Hardy, Wolff, and Goodell.[7] A pain of 4 dols is somewhat more painful than an ordinary pinprick. Before the experiments here reported were begun, each subject learned to estimate pain intensity in terms of the dol scale. The opening and closing of the shutter on the apparatus produced a click without transmission of heat; this was considered a "zero" stimulus. Stimuli above 350 mcal. per second per square centimeter for three seconds may produce tissue damage and were therefore avoided.

Skin resistances were measured with a modified vacuum-tube voltmeter, which was in series with the subject by means of two rectangular, chloridized silver electrodes attached to the palmar surface of the index and middle fingers of the right hand. The subject received 3 volts of direct current through a 200,000-ohm resistor. Cambridge electrode jelly was used on the skin, and the electrodes were taped at each end to secure insulation and uniformity of contact area.[29] Resistances were read directly from the voltmeter dial. The galvanic skin response was readily distinguished from the gradual changes in resistance which constantly occur in the skin. The error of reading the instrument is not greater than 5%, and kymographic records of skin resis-

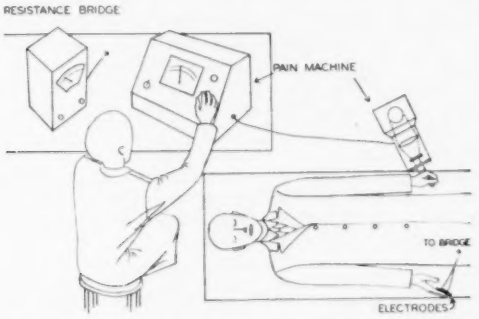

Fig. 1.—Experimental arrangement for observing the galvanic skin response to graded intensities of pain.

tance were not made, since Hardy found that these offered no significant advantages.[30] The galvanic skin response was calculated on the basis of the following equation:

$$\frac{dR}{R} = \text{per cent change in resistance (or galvanic skin response)}$$

where dR is the change in resistance, and R, the level of resistance just prior to the application of the stimulus. There is considerable discussion in the literature regarding the best means of expressing the galvanic skin response.[31] This simple calculation, used by Furer and Hardy and other investigators,[31b] is adequate to express the relatively gross changes in resistance seen in this type of experiment.

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29. Blank, I. H., and Finesinger, J. E.: Electrical Resistance of the Skin: Effect of Size of Electrodes, Exercise and Cutaneous Hydration, Arch. Neurol. & Psychiat. **56**:544, 1946.

30. Hardy, J. D.: Personal communication to the authors.

31. (*a*) Haggard, E. A., and Garner, W. R.: An Empirical Test of a Derived Measure of Changes in Skin Resistance, J. Exper. Psychol. **36**:59, 1946. (*b*) Hunt, W. A., and Hunt, E. B.: Comparison of Five Methods of Scoring Galvanic Skin Response, ibid. **18**:383, 1935. (*c*) Lacey, O. L., and Siegel, P. S.: An Analysis of the Unit of Measurement of the Galvanic Skin Responses, ibid. **39**:122, 1949.

During a 10-minute control period, the skin resistance was recorded every two minutes in order that the resting level should be obtained. After 10 minutes, the first stimulus was administered and the galvanic skin response observed. Each two minutes thereafter a more intense pain was induced. The order routinely followed was zero, threshold, and 2, 4, 6, and, in some cases, 7 dols. After each stimulus, the galvanic skin response was noted. After the last stimulus, the subject was asked to report the intensity of the pains perceived, according to the dol scale.

Hypnosis was then induced, visual fixation and suggestions of heaviness of the eyelids being used. Involuntary closure of the lids, with inability to reopen them, was considered the initial stage of the light trance. Depth of trance was estimated at each session by criteria other than analgesia. In general, the criteria were those of the Davis hypnotic susceptibility test, as described by Friedlander and Sarbin.[32] Phenomena of the light trance were held to include catalepsy of the lids, limb catalepsies, involuntary rigidity of the limbs, inhibitions of voluntary movements, and automatic movements. The criteria of medium trance included partial posthypnotic amnesia, simple posthypnotic suggestions, and hallucinations of heat and cold. The criteria for deep trance included ability to open the eyes without the trance being affected, production of visual and auditory hallucinations, complete posthypnotic amnesia, and posthypnotic hallucinations.

At each session, after hypnotic suggestions of anesthesia had been made, the thermal stimuli were repeated in the same order as in the control period, and the galvanic skin response was measured as before. While still hypnotized, the subject was asked to give his impressions of the pain induced by the stimuli, according to the dol scale. If pain had been perceived, an attempt was made again to measure the pain threshold, and the subject's ability to discriminate between stimuli of various intensities was noted. The subject was then awakened and asked to tell what he remembered of the hypnotic experience, particularly with regard to the pains perceived.

Every effort was made to keep the experimental conditions standardized. No conversation was permitted except for hypnotic suggestions and the questioning of the subject. The subject was asked to evaluate his mood and efficiency for the day at the conclusion of every experimental session. For control purposes, the periods of hypnosis and control were occasionally reversed with four of the seven subjects.

RESULTS

A general summary of the results is to be found in the Table. The subjects were numbered 1 to 7 on the basis of the average estimated depth of hypnotic trance achieved in each. Data were collected at 45 experimental sessions, during which 478 stimuli were administered, varying from painless shutter clicks to blister-producing intensities. At each session the subject's sensations during the control period were compared with his sensations following identical stimuli during the hypnotic period. Similarly, the galvanic skin response to each stimulus in the control period at a given session was compared with the galvanic skin response to the identical stimulus during the hypnotic period.

In order that the effects of hypnotic suggestion of anesthesia upon pain perception may be expressed quantitatively, it is desirable to define conditions of analgesia and hypalgesia. Analgesia is defined as that state in which none of the noxious stimuli administered were reported as painful. Hypalgesia is defined as a state in which noxious stimuli were reported as less painful than would be expected on the basis of reports of the same subject regarding the same stimuli in control situations. Hypalgesia can thus be measured as the difference between the reported and the expected pain intensities, expressed in dols. The dol is a unit of painfulness, and the entire scale of pain intensity, from threshold to maximal painfulness, encom-

32. Friedlander, J. W., and Sarbin, T. R.: The Depth of Hypnosis, J. Abnorm. & Social Psychol. **33**:153, 1938.

passes 10½ dols. This scale was derived from the observation that 21 just noticeable differences in pain intensity exist between the upper and the lower limit of painfulness, thus making each dol equivalent to two such differences, or roughly one-tenth the intensity of the maximal painfulness.

So that it might be determined whether the galvanic skin responses following hypnotic suggestions of anesthesia differ significantly from those of control period, the *t* ratios were calculated from the data on each subject, using matched pairs. Pairs were made of galvanic skin responses to identical stimuli administered in hypnotic and control periods at each session, and average differences were determined. This procedure eliminated any possible effects due to "adaptation" or "oscillation."

It was found that hypnotic suggestions of anesthesia generally produced a definite reduction in the galvanic skin response to noxious stimulation. For all

Effect of Hypnotic Suggestion of Anesthesia on Pain Sensation and on the Galvanic Skin Response to Pain

Subject No.	No. of Observations	Depth of Trance	Pain Perception	Reduction of Galvanic Skin Response, %	Degree of Confidence
1	28	Light	Unchanged	26	0.05
2	118	Light	Hypalgesia 0-2 dols	64	0.01
3	48	Light	Hypalgesia 0-4 dols	49	0.01
4	92	Light	Hypalgesia 0-6 dols	55	0.01
5	10	Light	Hypalgesia 5 dols	67	0.01
	100	Medium	Analgesia		
6	50	Medium	Hypalgesia 5 dols	57	0.01
		Medium	Analgesia		
7	42	Medium	Hypalgesia 6 dols	62	0.01
		Deep	Analgesia		

but Subject 1, the *t* ratio was found to be significant above the 1% level of confidence, indicating that the reduction in galvanic skin response was definitely related to some aspect of the hypnotic situation rather than to the operation of chance factors in the experiment. Since Subject 1 had such a small number of trials, the *t* ratio was less; yet the reduction of 26% is significant above the 5% level of confidence.

SUBJECT 1.—At each session, the subject reacted to the induction of hypnosis with anxiety, the chief signs of which were increased pulse rate, respiration rate, and cardiac thrust. Such reactions have been described by Schneck.[33] It is noteworthy that on every occasion he achieved only a light trance and at no time reported analgesia or hypalgesia; indeed, on several occasions he reported a higher dol value for stimuli in the hypnotic state than in the control period. Nevertheless, there was still a definite reduction in the galvanic skin responses during the hypnotic period.

SUBJECT 2.—This subject knew the experimental plan, including the proposed intensities of thermal stimuli to be given during each period. A light trance was produced at each session. Figure 2 indicates that the perception of pain was not greatly affected, although hypalgesia for

33. Schneck, J. M.: Psychosomatic Reactions to the Induction of Hypnosis, Dis. Nerv. System **11**:118, 1950.

the higher stimuli occurred. In this Figure, based entirely on the subject's reports, some interesting findings are obscured. At five sessions attempts were made to remeasure the pain threshold before terminating hypnosis. At two of these sessions, the threshold was unchanged, and the reports were reproducible and consistent with those given in accordance with the routine procedure. At a third session, the threshold was found to be elevated 15%, although the routine reports indicated that there had been no elevation. In the remaining two sessions, the reports on remeasurement of the pain threshold were extremely variable. For example, the subject reported a thermal stimulus of 300 mcal. as "1 dol," but 275 mcal. as "almost 2." During these periods the subject had no idea of the order in which stimuli were being administered. Therefore, in three of the five trials the subject's ability to discriminate accurately among different thermal stimuli was definitely affected.

On one occasion hyperesthesia of the left arm was suggested. No galvanic skin response was obtained to thermal stimuli administered in the usual order, although significant responses had been obtained during the control period. However, the subject winced; and when a stimulus usually evoking a 4-dol pain was given, she withdrew her arm from the aperture of the pain machine. Pain discrimination, as judged by remeasurement of the pain threshold with the subject under hypnosis, was not affected, although she reported that "he made my arm red, flushed, and painful."

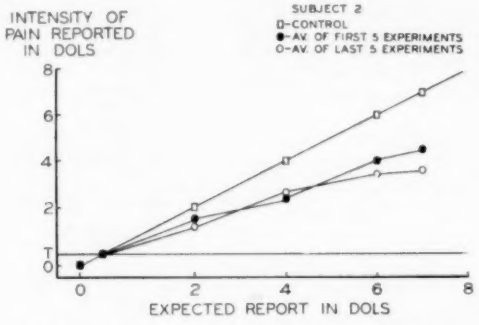

Fig. 2.—Influence of hypnotic suggestion of anesthesia upon pain perception. Hypalgesia was produced for more intense pains with no alteration in pain threshold.

Although hypalgesia was slight, and only a light trance could be achieved, a relatively strong effect of hypnotic suggestion on the galvanic skin response was seen.

Subject 3.—This subject gave somewhat variable reports during the control periods. A light hypnotic trance was produced at each session. Hypalgesias as a result of hypnotic suggestion were more pronounced in the first two sessions (the reverse of the tendency noted in Subjects 4, 5, 6, and 7). Adaptation to the experimental situation was rapid, with the control galvanic skin response nearly disappearing by the fourth session. Despite these findings, the galvanic skin responses to pain following hypnotic suggestions were on the average less than one-half as great as those in the control period.

Subject 4.—At the first three sessions, this subject, like Subject 1, reacted with anxiety to induction of hypnosis. A light hypnotic trance was produced at each session. In seven of the nine trials in which anesthesia of the left hand was suggested, there was elevation of the pain threshold with the subject under hypnosis, and hypalgesia extended through 6 dols. On six occasions the pain threshold was remeasured when the subject was under hypnosis, and in some instances discrimination was found to be affected.

On one occasion hyperesthesia was suggested. Pain discrimination was affected, but the stimuli were not perceived as any more painful than during the control period, and the galvanic skin response averaged 28.6% less than the control.

SUBJECT 5.—The results obtained in this subject parallel the depth of hypnotic trance achieved (Fig. 3; dotted line represents the expected reports). During the first five trials, with light trances, hypalgesia for the stimuli of higher intensity was noted, and remeasurement of the threshold indicated that there had been a significant elevation in all but one instance. In this case the subject's pain discrimination had been affected. None of the administered stimuli were perceived in the sixth and seventh trial, when a medium depth of trance was achieved. In the last three trials, the depth of trance was somewhat lighter, and the higher-intensity stimuli were again reported as painful, but with definite hypalgesia. This subject, when successful suggestions of anesthesia were made during the two trances of medium depth, had no galvanic skin response to stimuli up to 300 mcal. (which had produced 6-dol pain in the control period).

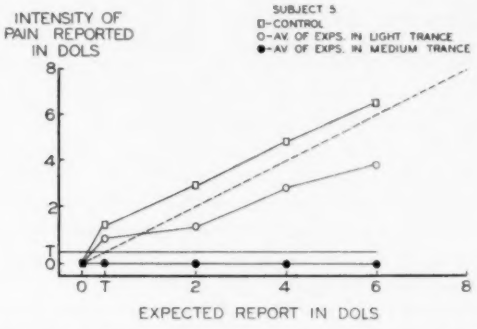

Fig. 3.—Hypalgesia and analgesia produced by suggestion of anesthesia in light and medium trances, respectively.

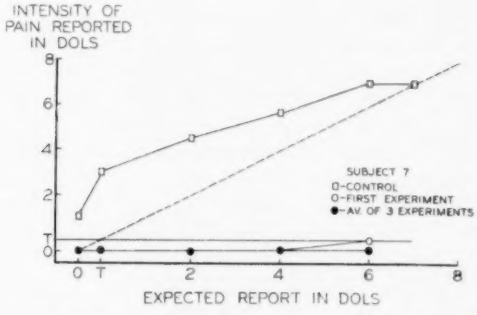

Fig. 4.—Analgesia resulting from hypnotic suggestion of anesthesia.

SUBJECT 6.—A medium depth of trance was produced at each session. In only one of the five trials did this subject perceive any of the thermal stimuli administered during hypnosis. In this one, he reported the stimuli normally evoking 6 and 7 dols as "2 dols." Otherwise, there was no report of pain. On one occasion, during the period of hypnosis there was no galvanic skin response at all to any of five stimuli ranging up to 330 mcal. (which produced 6-dol pain in the control period).

SUBJECT 7.—In the first experiment, this subject reported stimuli normally evoking 6 dols as "threshold," but in the remaining three experiments she reported no pain. She was judged to be in a trance of medium depth on the first occasion and in a deep trance in the last three experiments. These results are illustrated in Figure 4.

COMMENT

As a result of hypnotic suggestions of anesthesia, the following effects on sensation were observed: (1) no alteration in reports of pain intensity; (2) hypalgesia for higher-intensity stimuli without elevation of the pain threshold; (3) definite elevation of pain threshold with hypalgesia; (4) analgesia; (5) disturbances in pain discrimination.

The third effect was observed in the majority of trials. The threshold elevation in light trances may be similar to that which can be produced by suggestion in the unhypnotized subject,[8] but in deeper trances the effectiveness of hypnotic suggestion is much greater. The progression of effects 1 through 4 appears to be directly related to the depth of trance. The fifth effect was variable and was seen only in conjunction with the third effect. It is described as a separate phenomenon because the disturbance of ability to discriminate relatively between stimuli of differing intensities was only clearly observed when we were remeasuring pain thresholds. In actuality, it may merely represent a facet of altered pain perception, and the variability of its appearance may be related to the variable psychological state of the subject. It must be kept in mind that the hypnotic trance is not a static state. It is influenced by the many internal and external stimuli which constantly affect the subject. For example, the repetition and reinforcement of suggestions of anesthesia during hypnosis is an important variable factor. The depth of trance may vary within a single 20-minute session, and there is certainly a variability in depth of trance from one session to the next. Our gross classification of depth of trance serves only as a general guide. The personality of the individual subject also plays an important role. Thus, in Subject 3 there was a decreasing effectiveness of the suggestions of anesthesia in successive hypnotic sessions, whereas Subjects 2, 4, 6, and 7 showed the opposite trend. Subject 5 achieved a trance of medium depth in the sixth and seventh sessions, and on these two occasions analgesia was observed. Yet, on three subsequent occasions, the trance was not as deep, and hypalgesia was variable, although greater than in the first five sessions. In subjects who demonstrated analgesia for stimuli up to 355 mcal. per second per square centimeter, one must consider the possibility that stimuli of higher intensities (evoking pain of 8 to 10½ dols in the control state) might have been perceived. Such stimuli were not used because of the danger of producing skin damage.

The galvanic skin response provides a relatively simple measurement of sympathetic nervous activity. But here, too, the operation of many variables must be considered: Physiological factors influence the automatic nervous system, skin temperature, resting level of skin resistance, general psychological status, and attitude toward the experiment; all these play some role, making it necessary to use statistical methods to clarify the meaning and significance of the experimental data. A review of the literature reveals no evidence that the hypnotic state per se affects the galvanic skin response. Controls in the experiments by Sears [24] do not indicate any influence of hypnotic trance alone upon the galvanic skin response; this is borne out by the observations of Brown and Vogel.[26] An experiment with two controls, one waking and one in trance without suggestion of anesthesia, was done at the beginning of the present study and confirmed

the above observations. The recent studies by Ravitz,[34] published since the completion of the present experiments, need not alter this view. Ravitz found changes in direct-current potential differences between the forehead and the palm in hypnosis as compared with the waking state. Even though the galvanic skin response has both a resistance and a potential component, it is unlikely that the small potential difference found by Ravitz could play a significant role in the relatively large changes in skin resistance seen in the galvanic skin response to noxious stimulation.

From the practical point of view two special characteristics of the galvanic skin response deserve special mention: The first is the phenomenon of oscillation, which is observed in any experiment which measures the galvanic skin responses to serial stimuli. The second is the phenomenon of adaptation, which occurs according to a definite pattern when data from many subjects are studied statistically, but which may be quite variable from one individual to another. In our group, Subject 3 had almost completely adapted by the fourth session, showing little galvanic skin response to noxious stimulation even in the control period. Subject 2, on the other hand, had an atypical adaptation curve, with a tendency to increasing intensity of galvanic skin response as the experiment progressed. Other subjects showed the expected gradual adaptation curves. The experiment was constructed to eliminate the effects of these phenomena upon the significance of the results, so that their influence is distributed equally over control and experimental figures. Inspection of the raw data indicates that oscillation and adaptation affect the galvanic skin response during hypnosis and during the control periods in the same general way.

The experimental results leave no doubt that hypnotic suggestion diminishes the galvanic skin response to noxious stimuli. This is related to, but not dependent upon, the effectiveness of the suggestion of anesthesia per se. Thus, in Subject 2, with only moderate hypalgesia, the galvanic skin response to noxious stimulation was diminished by 64%; in Subject 6, with analgesia on nearly all trials, only 57%. It is particularly interesting that Subject 1 had a reduction in galvanic skin response of 26% after hypnotic suggestions which apparently had no effect upon his pain perception, and which seemed even to make him anxious. Subject 5 showed a direct correlation between depth of trance and decrease of galvanic skin response, while Subjects 6 and 7 showed no such correlation. Toward the end of the experiment attempts were made to restore the galvanic skin response, or to increase it over control levels, by suggesting hyperesthesia. Such suggestions were couched in terms of increased sensitivity of the skin due to sunburn or scalding. Subjects 2, 4, and 5 were studied in this respect, and all trials were unsuccessful. Factors of adaptation and conditioning may be responsible for this finding.

It is important to realize that on some occasions hypnotic anesthesia apparently led to complete disappearance of the galvanic skin response to all stimuli during a given session, such stimuli evoking pain of 6 or 7 dols in the control period. This phenomenon was seen twice with Subject 3, twice with Subject 5, and once with Subject 6. In several trials there was only a very slight galvanic skin response

34. Ravitz, L. J.: Standing Potential Correlates of Hypnosis and Narcosis, A. M. A. Arch. Neurol. & Psychiat. **65**:413, 1951.

to the higher stimuli during hypnosis. In all the control periods there was only one occasion on which a stimulus evoking pain of 6 or 7 dols failed to produce a galvanic skin response, while equally intense stimulation failed to produce a galvanic skin response on 14 occasions after hypnotic suggestions of anesthesia. This observation is stressed because it suggests a need for caution in the clinical use of the galvanic skin response to distinguish organic from hysterical anesthesias.

SUMMARY

A study is reported in which pain perception and galvanic skin responses of seven subjects were measured before and during hypnosis. The depths of hypnotic trance varied from light to deep. Stimuli of measured intensity were administered, and changes in pain threshold were measured. Quantitative estimates of pain intensity were made by the subjects. Alterations in ability to discriminate between pains of differing intensities were noted. Quantitative records of galvanic skin responses were utilized, permitting statistical analysis of data from matched pairs.

Data were collected at 45 experimental sessions, during which a total of 478 painful stimuli were administered, the stimuli varying in intensity from threshold to blister-producing levels. At each session, the subject's sensations from and responses to stimuli during a control period were compared with sensations from and responses to identical stimuli administered after hypnotic suggestions of anesthesia.

The following observations were made:

1. Hypnotic suggestions of anesthesia influence pain perception by causing elevation of pain threshold, hypalgesia, and analgesia.

2. When hypnotic suggestions of anesthesia caused hypalgesia and elevation of pain threshold, ability to discriminate among stimuli of different intensities was impaired.

3. There was a general correlation between the depth of hypnotic trance and the degree to which pain perception was altered by hypnotic suggestion.

4. The galvanic skin response to noxious stimulation was diminished, and it sometimes disappeared, as a result of hypnotic suggestions of anesthesia. The galvanic skin response was affected even when there was no alteration in pain perception, according to subjective reports.

BLOOD CLOTTING IN PATIENTS WITH MENTAL DISEASES BEFORE AND AFTER TREATMENT

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ACCELERATION of blood-clotting time in patients with schizophrenic, manic-depressive, or involutional psychosis has been recognized for many years; not all patients with these disorders exhibit this phenomena.[1] Changes in clotting in relation to shock treatment have not been described; it was considered desirable, therefore, to study the effects of such treatments on the clotting of blood.

MATERIAL AND METHODS

Clotting time was studied by the method of Lee and White [2] in 21 patients before, and again several days after, a course of insulin or electroshock treatment. The recalcified clotting time [2] was studied similarly in 40 other patients; observations on the recalcified clotting time also were made in 20 of these patients immediately before, 10 minutes after, and 4 hours after, an electroshock treatment. The diagnoses included schizophrenia and manic-depressive and involutional psychoses. Forty-two of the 61 patients studied were women; the ages of the patients ranged from 18 to 68 years.

Control observations consisted of 50 measurements of clotting time and 25 measurements of recalcified clotting time in normal subjects.

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1. (*a*) Hauptmann, A.: Die Beschleunigung der Blutgerinnungszeit bei Katatonie, Ztschr. ges. Neurol. u. Psychiat. **29**:323, 1915. (*b*) Bumke, H.: Die Beschleunigung der Blutgerinnungszeit bei Dementia praecox, Monatsschr. Psychiat. u. Neurol. **40**:344, 1916. (*c*) Schneider, E.: Zur Frage der Blutgerinnungszeit bei der Dementia praecox, ibid. **45**:55, 1919. (*d*) Hertz, A.: Über die Veränderung der Blutgerinnungszeit bei Dementia praecox, Arch. Psychiat. **71**:452, 1924. (*e*) Büchler, P.: Leberfunktionsstörungen bei Geistes- und Nervenkranken, ibid. **73**:610, 1925; (*f*) Uber Störungen der Blutgerinnung bei Geistes- und Nerven-krankheiten, Zentralbl. Neurol. **41**:280, 1925. (*g*) Forrest, J. R.: Blood Coagulation Time in the Insane, Brit. M. J. **1**:777, 1925. (*h*) Schrijver, D., and Schrijver-Hertzberger, S.: Untersuchungen über die Blutkorperchensenkungsreaction, Blutgerrinung und Fibrinogengehalt des Plasma bei Psychosen, Ztschr. ges. Neurol. u. Psychiat. **117**:773, 1928. (*i*) Johannes, T.: Blutgerinnungszeit und psychiatrische Diagnostik, Arch. Psychiat. **78**:165, 1928. (*j*) Goldkuhl, E.; Kafka, V., and Orstrom, A.: Zur Biologie der Schizophrenie, Acta psychiat. et neurol., Supp. **47**:118, 1947. (*k*) Arnold, O. H.: Untersuchungen zur Frage der akuten tödlichen Katatonien, Wien. Ztschr. Nervenh. **2**:386, 1949.

2. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Ed. 11, Philadelphia, W. B. Saunders Company, 1948.

OBSERVATIONS

Values for blood-clotting time were below the lowest normal reading in only 10% of the untreated psychotic patients; however, the distribution of values shows that probably twice that number of patients have acceleration of clotting (Chart 1). No consistent changes occurred after a course of electroshock or ambulatory insulin

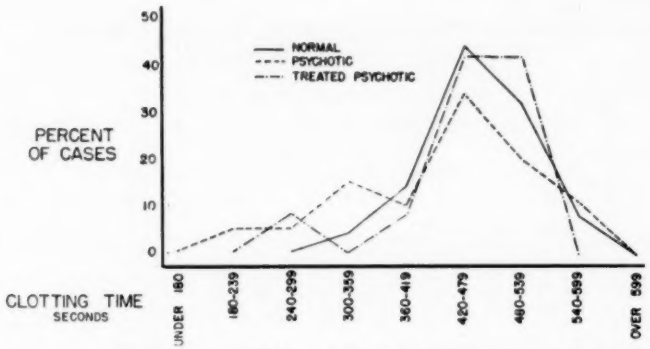

Chart 1.—Clotting time (Lee-White method) in patients before and after a course of insulin or electroshock treatments.

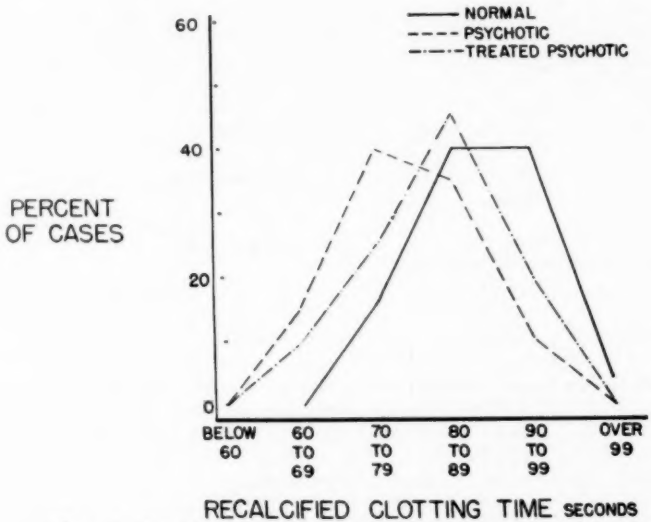

Chart 2.—Recalcified clotting time in patients before and after a course of insulin or electroshock treatments.

treatments in patients who initially had normal clotting times; the times became normal in most of the patients in whom accelerated clotting existed before treatment (Chart 1).

Fifteen percent of the patients studied before treatment showed recalcified clotting times below the lowest normal values (Chart 2); however, the distribution of

these measurements showed that a third of the untreated psychotic patients probably had abnormally accelerated clotting times. The recalcified clotting times were still accelerated in a sixth of the patients after a course of electroshock or ambulatory insulin treatments (Chart 2).

When measurements of recalcified clotting time were made before and after single electroshock treatments, acceleration was found at both 10 minutes and 4 hours, but not 48 hours, after the treatments (Chart 3).

COMMENT

The finding of accelerated blood clotting in about a fifth of patients with schizophrenic, manic-depressive, and involutional psychoses is in corroboration of earlier work [1]; no evidence was found of differences in clotting times among the different diagnostic categories. The work of Goldkuhl and associates,[1j] which demonstrated acceleration of the recalcified clotting time in patients with schizophrenia, has been

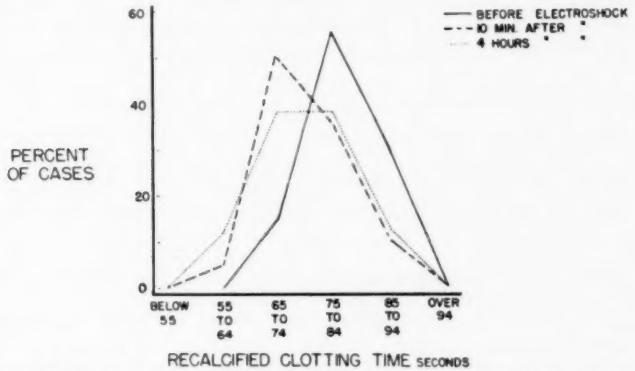

Chart 3.—Effect of a single electroshock treatment on recalcified clotting time.

extended in the present work to include the other diagnostic categories; about a third of the patients studied here had rapid recalcified clotting times, irrespective of the diagnostic categories.

The mechanism of the changes found is not clear. Goldkuhl and associates [1j] described increased thrombin activity, of unspecified cause, in the blood of schizophrenic patients; fibrinogen contents have been reported as normal, or sometimes increased.[3] Bleeding times also are shortened.[4] The fact that accelerated clotting commonly occurs in patients who are obviously tense or agitated raises the question whether increased production of epinephrine may be a factor; that substance has long been known to accelerate clotting in some unknown manner in mammals,

3. Schrijver, D., and Schrijver-Hertzberger, S.: Über die Blut-Eiweisskörper im schizophrenen Formenkries, Ztschr. Neurol. u. Psychiat. **140**:252, 1932; footnote 1*h*. Goldkuhl, Kafka, and Orstrom.[1j] Riebeling, C., and Stromme, R.: Studien zur Pathophysiologie der Schizophrenie, Ztschr. ges. Neurol. u. Psychiat. **147**:61, 1933.

4. Uyematsu, S.: The Platelet Count and Bleeding Time in Catatonic Dementia Praecox, Am. J. Psychiat. **1**:15, 1921.

including man.[5] However, the fact that clotting is not abnormal in neurosis [6] is against the concept that emotional upset alone causes the changes observed. The observation that patients with the psychoses discussed here commonly exhibit evidence of hyperactivity of the adrenal cortex [7] raises the possibility that hormones produced by it may play a part. There is no agreement, however, concerning the effects of adrenocortical hormones on clotting of blood.[8] It is evident that the data available are not sufficient to explain the rapid clotting of blood that occurs in many patients with mental disease. The acceleration of blood clotting that occurs after each electroshock treatment likewise cannot be explained on the basis of available knowledge. The hemoconcentration noted during electrically induced convulsions [9] is of minor and passing significance, as the changes persist only 10 to 30 minutes. The probability that an outpouring of epinephrine occurs during each shock treatment [10] might explain the acceleration of recalcified clotting time found 10 minutes after each treatment (Chart 3). However, the persistence of the observed changes for four hours indicates that other factors must be present.

Acceleration of blood clotting in psychotic patients may give rise to intravascular thrombosis under some circumstances. The occurrence of phlebitis and pulmonary embolism as complications of prolonged barbiturate narcosis has been described [11]; circulatory stagnation caused by the barbiturate used probably is important in this connection. The fact that intravascular thrombosis rarely occurs in association with electroshock treatments, in spite of the further shortening of clotting time observed after these treatments, is probably due to the marked acceleration of circulation that occurs at the same time.[12] A similar interpretation may explain the rarity of intravascular thrombosis [13] in patients receiving insulin therapy.

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11. Palmer, H. A.: Thrombo-Phlebitis Occurring in Patients Receiving Barbiturates: An Unrecorded Complication of Sleep Treatment, J. Ment. Sc. **85**:276, 1939. Clapp, J. S., and Loomis, E. A., Jr.: Continuous Sleep Treatment: Observations on the Use of Prolonged, Deep, Continuous Narcosis in Mental Disorders, Am. J. Psychiat. **106**:820, 1950.

12. Altschule, M. D.; Sulzbach, W. M., and Tillotson, K. J.: Significance of Changes in the Electrocardiogram After Electrically Induced Convulsions in Man, Arch. Neurol. & Psychiat. **58**:717, 1947.

13. Donnelly, J., and Radley-Smith, E. J.: Thrombotic "Hydrocephalus" in Insulin Therapy, Lancet **2**:904, 1950.

SUMMARY AND CONCLUSIONS

Acceleration of clotting time and of recalcified clotting time of blood are common in untreated patients with schizophrenic, manic-depressive, and involutional psychoses. Individual shock treatments give rise to temporary further acceleration of clotting in these patients.

Patients in whom accelerated clotting is found before treatment usually exhibit normal clotting when studied several days after the end of a course of insulin or electroshock treatments.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

STRUCTURE OF THE GOLGI APPARATUS OF SPINAL GANGLION CELLS AS SHOWN BY APPLICATION OF DESILVERING METHODS TO STANDARD DA FANO PREPARATIONS. F. B. ADAMSTONE, J. Morphol. **90**:201 (March) 1952.

By use of a dilute solution of iodine, nerve ganglion cells which had been impregnated with silver by the Da Fano modification of Cajal's technique were destained so as to reveal finer structural details of the Golgi apparatus.

The application of this method showed that in nerve cells the typical Golgi net of metallic-silver impregnations was not an artifact, but was actually a fragmentary demonstration of a structure consisting of (1) a net-like cytoplasmic reticulum and (2) a series of minute, silvered granules closely applied to the surface of the net.

The reticulum material retained a deeper golden color on destaining, in contrast to the pale yellow of the surrounding cytoplasm. Clear, apparently empty areas in the segments indicated that the reticulum was a hollow canal. Although the material of the reticulum stained readily with silver, it was less resistant to desilvering than the associated granules.

Adamstone concludes that the fixed and silvered classic Golgi apparatus of nerve cells is a canalicular cytoplasmic reticulum with which mitochondria are closely associated. The mitochondria become blackened first during silver impregnation and thus serve as centers from which the silvering spreads.

This method of destaining should be useful in determining the nature of structures in other cells that have been identified as Golgi bodies.

REID, New Brunswick, N. J.

A STUDY OF THE GOLGI APPARATUS IN SPINAL GANGLION CELLS OF THE PIG USING FRESH FROZEN SECTIONS. F. B. ADAMSTONE and A. B. TAYLOR, J. Morphol. **90**:217 (March) 1952.

A new method for the preparation of fresh frozen-tissue sections of spinal ganglion cells was developed to insure rapid, uniform fixation, so that structural changes due to shrinkage and postmortem changes due to slow penetration of the fixative might be eliminated.

From the study of such preparations the authors draw the following conclusions: 1. The silver-impregnated Golgi network of standard preparations of spinal ganglion cells is the combined result of, first, the silvering of many minute granules, followed by the further silvering of cytoplasmic strands associated with these granules. The standard silvered network is an imperfect image, enhanced by shrinkage, of two closely associated components. 2. In frozen sections, silvering or any other staining method appears to affect numerous minute granules, before any other cellular element is stained. These granules appear to be mitochondria. In Altmann fluid-fixed material, which is treated by prolonged osmication, the cytoplasmic reticulum is well defined. However, in silver preparations and in Altmann mitochondrial preparations, the reticulum with which the granules are associated is less clearly defined, but its presence is unmistakable. From the study of frozen sections it has been impossible to decide whether or not the reticulum is a canalicular structure.

Adamstone and Taylor conclude from this study of both standard and frozen sections that the classic fixed, silvered Golgi apparatus of spinal ganglion cells is actually a combination of a cytoplasmic reticulum with some of the mitochondria of the cell.

REID, New Brunswick, N. J.

Physiology and Biochemistry

PATHOLOGIC LESIONS IN THE NERVOUS SYSTEM OF THE DUCK FED A RATION DEFICIENT IN VITAMIN A. R. H. RIGDON, A. M. A. Arch. Path. **53**:239, 1952.

Numerous observations have been made on the neurologic manifestations of vitamin-A deficiency; however, there are now two opposing views relative to this mechanism. One group of workers believes that a degenerative change occurs in the central nervous system and in the peripheral nerves, whereas Wolbach and Bessey believe that the lesions in the nervous system result from a mechanical distortion produced by a differential rate of growth between the vertebrae and the spinal cord, resulting in pressure on the spinal nerves.

Rigdon reports additional studies on the pathologic changes observed in ducks fed a ration deficient in vitamin A. The changes occurring in young ducks fed a vitamin-A-deficient ration are found primarily in the nerve cells of the spinal cord and the spinal root ganglia. Few petechiae are present in the gray substance of the cord. The vertebral column was carefully examined to see whether the osseous tissue had compressed the cord. Such pressure was not demonstrated.

WINKELMAN, Philadelphia.

INHIBITION OF GROWTH OF FIVE TRANSPLANTABLE MOUSE TUMORS BY THE VIRUS OF RUSSIAN FAR-EAST ENCEPHALITIS. A. E. MOORE, Cancer **4**:375 (March) 1951.

Previous work had shown that the transplantable mouse sarcoma 180 can be destroyed completely in the process of infection with the virus of Russian Far-East encephalitis. Moore has studied the effects on other tumors in mice. Complete inhibition of tumor growth occurred in methylcholanthrene-induced fibrosarcoma MCI. Adequate concentrations of the virus killed all the viable tumor cells of mammary adenocarcinoma EO 771 and prevented growth on transplantation of the Ridgway osteogenic sarcoma and sarcoma T241. Neuroblastoma C 1300 was the most susceptible of the five tumors studied. It was found that when 0.05 cc. of a 10^{-5} virus dilution was inoculated intraperitoneally a tumor removed five days later and two tumors removed eight days later failed to grow. Five days after inoculation the titer of the virus in the tumor was greater than $10^{-9.0}$, while that in the brain was $10^{-6.0}$.

FOLEY, Boston.

TESTOSTERONE PROPIONATE AS A NITROGEN-SPARING AGENT AFTER SPINAL CORD INJURY. I. S. COOPER, E. H. RYNEARSON, C. S. MACCARTY, and M. H. POWER, J. A. M. A. **145**:549 (Feb. 24) 1951.

One of the most difficult problems in the management of severe injuries to the spinal cord is the maintenance of adequate nutritional status. Forced feedings and parenteral administration of plasma, whole blood, or amino acids have not been universally successful in the solution of the problem of protein depletion. The present report considers the possible usefulness of testosterone propionate as an anticatabolic, or nitrogen-sparing, agent in patients who are paraplegic after trauma to the spinal cord, and includes observations on the excretion of nitrogen and the development of decubitus ulcers.

The catabolic effect of trauma to the spinal cord was studied in a control group of 15 patients. A second group of 15 patients was studied after injury to the spinal cord. Each patient received the same treatment as that afforded subjects in the control groups except for the additional measure of the administration of testosterone propionate in varying dosage. The dose most frequently used was 50 to 100 mg. a day, administered intramuscularly.

The 15 patients who received testosterone propionate after severe trauma to the spinal cord demonstrated considerably less urinary excretion of nitrogen and creatine, a more favorable status of nitrogen balance, less pronounced hypoproteinemia, and a lower incidence of decubitus-ulcer formation than did the control group. The effect of testosterone compounds on the disuse atrophy of bone, pathological calcification of soft tissues, and incidence of urinary calculi in paraplegic patients merits evaluation.

ALPERS, Philadelphia.

ANTICONVULSIVE PROPERTIES OF DESOXYCORTICOSTERONE. R. B. AIRD and G. S. GORDAN, J. A. M. A. **145**:715 (March 10) 1951.

The anticonvulsant effects of desoxycorticosterone acetate have been demonstrated repeatedly in animals. In order that its anticonvulsant activity might be tested clinically, desoxycorticosterone acetate was administered as sublingual tablets, in doses varying from 4 to 15 mg. a day, to 10 patients whose convulsive seizures were inadequately controlled on standard anticonvulsant regimens. Because these patients had proved refractory to previous anticonvulsant therapy, desoxycorticosterone acetate was added to those combinations of other agents that had been found helpful.

When desoxycorticosterone acetate was added to the regimen, the attacks became less frequent in seven patients; the medication appeared to benefit the petit mal spells in six of these patients and the grand mal seizures in two of them. In two instances seizures were entirely abolished. Substitution of placebo tablets in the group that appeared to be benefited by desoxycorticosterone acetate resulted in a dramatic resumption or increase in the number of seizures in two patients and in almost status epilepticus in one patient. Reinstitution of the hormonal therapy in these patients again resulted in amelioration of the convulsive tendency. During the period of treatment with desoxycorticosterone acetate there was no significant increase in blood pressure or weight or any evidence of edema.

Administration of the water-soluble conjugate desoxycorticosterone glucoside tended to reduce the incidence of abnormal waves in the electroencephalogram.

These data suggest that desoxycorticosterone acetate, at least when used as an adjuvant to other anticonvulsant therapy, possesses anticonvulsant properties for petit mal and possibly, to some extent, for grand mal.

ALPERS, Philadelphia.

BIOCHEMISTRY OF THE SPHINGOLIPIDES: V. STRUCTURE OF SPHINGINE. H. E. CARTER and C. G. HUMISTON, J. Biol. Chem. **191**:727, 1951.

In 1916 Levene and West reported that chemical reduction of dihydrosphingosine yielded an optically active base sphingine, which they considered to be an amino alcohol, but which they did not characterize further. Recently, Carter and associates discovered that catalytic reduction of triacetylsphingosine produced acetic acid, presumably as a result of the hydrogenolysis of the allylic acetoxyl group. A convenient method has been developed for the preparation of diacetylsphingine by catalytic reduction of triacetylsphingosine. The structure of sphingine has been established as 1-hydroxy-2-aminooctadecane by oxidation of the N-benzoyl derivative to (—)-benzoyl-α-aminostearic acid. It has been discovered that acyl derivatives of D- and L-amino acids show characteristic changes in optical rotation on dilution of their dioxane or acetic solutions with water. These data appear to afford a new method of correlating the configuration of amino acids with their optical properties. On this basis, the (—)-benzoyl-α-aminostearic acid obtained from sphingine has been assigned the D configuration.

PAGE, Cleveland.

PROTEOLIPIDES, A NEW TYPE OF TISSUE LIPOPROTEINS: THEIR ISOLATION FROM BRAIN. J. FOLCH and M. LEES, J. Biol. Chem. **191**:807, 1951.

Tissues contain substances to which the name of proteolipides has been given. These are lipoproteins which exhibit solubilities quite different from the solubilities of other known lipoproteins. Thus, while the latter are usually soluble in water or dilute salt solutions, proteolipides are insoluble in water and freely soluble in chloroform-methanol-water mixtures. Proteolipides are present in the following tissues that have been studied, and which are listed in order of decreasing content of proteolipides: white matter of the brain, brain tumors, gray matter of the brain, heart, kidney, liver, lung, smooth muscle, and skeletal muscle. They are absent from blood plasma. From white matter three different proteolipide fractions have been isolated. One of them has been consistently obtained as a crystalline compound. The other two are birefringent powders. All three are insoluble in water and soluble in chloroform-methanol-water mixtures. Their protein moieties contain 1.76% S and are resistant to the action of trypsin.

PAGE, Cleveland.

ISOLATION OF BRAIN STRANDIN, A NEW TYPE OF LARGE MOLECULE TISSUE COMPONENT. J. FOLCH, S. ARSOVE, and J. A. MEATH, J. Biol. Chem. **191**:819, 1951.

From brain tissue a substance of high molecular weight has been isolated, to which the name of strandin has been given because, on drying from aqueous solutions, it forms strands which show good orientation under polarized light. It is freely soluble in water and chloroform. It is extracted from tissue with a 2:1 chloroform-methanol mixture by volume. It is especially abundant in gray matter. Strandin contains 2.6% nitrogen, less than 0.2% phosphorus, and less than 0.2% sulfur. It contains less than 1.5% neuraminic acid. Among its constituents are fatty acids, sphingosine or a sphingosine-like substance, carbohydrate, a primary amine which is combined in strandin through its NH_2 group, and a chromogenic group. The last-mentioned group is destroyed quantitatively, with production of brown color, on heating with 6 N hydrochloric acid at 100 C. for 15 minutes. This has been used for the development of a method for the estimation of strandin. Strandin has been prepared by three different methods. Essentially identical products have been obtained. They are all electrophoretically homogeneous, and in the ultracentrifuge they show a main component (80%) with a minimal possible molecular weight of 250,000.

PAGE, Cleveland.

ORIGIN OF THE ISOOCTYL SIDE CHAIN OF CHOLESTEROL. J. WUERSCH, R. L. HUANG and K. BLOCH, J. Biol. Chem. **195**:439, 1952.

Cholesterol synthesized in rat liver from either 1-C^{14} acetate or 2-C^{14} acetate was degraded to permit separate isotope analysis of the carbon atoms of the isooctyl side-chain. Five of the side-chain carbon atoms are derived from methyl groups of acetic acid, and three, from acetate carboxyls. The authors discuss the possibility that five carbon units related to isoprene are intermediates in the biosynthesis of cholesterol from acetic acid.

PAGE, Cleveland.

DELAYED RESPONSE PERFORMANCE OF MONKEYS WITH FRONTAL REMOVALS AFTER EXCITANT AND SEDATIVE DRUGS. J. S. BLUM, K. L. CHOW, and R. A. BLUM, J. Neurophysiol. **14**:197 (May) 1951.

Four young adult monkeys with removals of frontal granular cortex (two with additional ablations of posterior neocortex) were tested on the delayed-response problem while under the influence of sedative or excitant drugs (pentobarbital and amphetamine). Control injections of isotonic saline solution were also made. There were no significant differences in level of achievement under the various experimental conditions, although both pentobarbital and amphetamine reduced activity. Neither drug had differential effects on the frontal as opposed to frontal-posterior preparations.

The discrepancy between these results and those reported previously by other investigators is interpreted in terms of the length of time which had elapsed since operation (six months in the present series, as compared with three months in Wade's and Pribram's experiments). The authors suggest that sedatives may hasten adaptation to the delayed-response situation, an adjustment which would normally take place in the course of time, but that they have no effect on the associative process, which must occur anew at each trial.

ALPERS, Philadelphia.

Neuropathology

METASTASIZING CEREBELLAR TUMORS: DIFFICULTY IN DISTINGUISHING BETWEEN MEDULLOBLASTOMA AND NEUROBLASTOMA. ROBERT P. BARDEN and FREDERIC H. LEWEY, J. Neurosurgery **6**:439 (Nov.) 1949.

Barden and Lewey report three cases of cerebellar tumors which were associated with tumors of similar type outside the central nervous system.

In the first, that of a white woman aged 32, radium was implanted in the right cerebellar hemisphere in 1919. In 1921 a medulloblastoma was partially removed surgically, and again the hemisphere was irradiated. Two years later roentgenograms showed an extensive lesion involving both iliac bones, the sacrum, and the right femur. Review of the original slides in

1942 led to revision of the diagnosis to neuroblastoma. Thus, one of the cases of so-called metastasizing medulloblastoma was removed from the literature.

In the second case, that of a white boy aged 13, a tumor was removed from the left cerebellar hemisphere in 1938. The original diagnosis of "medulloblastoma" was made with reservations. The patient received roentgen therapy, but three years later there developed a growth of the left femur, which might have been a Ewing tumor.

In the third case, that of a white boy aged 14, a midline cerebellar tumor was removed in 1945. The pathologic diagnosis was that of a highly differentiated medulloblastoma. The patient was given radiation therapy, and 14 months later roentgenograms showed widespread destruction of bone. Biopsy was interpreted as showing neuroblastoma.

The authors believe that there may be two types of medulloblastoma: one, a very malignant form, found in children, and the other, less malignant, more frequently seen in adults. There is also the possibility that some of the cerebellar tumors in the older age group may be neuroblastomas rather than medulloblastomas. It is conceivable that a cerebellar tumor might represent metastasis from an occult primary tumor outside the central nervous system. The problem is far from solved.

TOZER, Philadelphia.

Meninges and Blood Vessels

ROLE OF SMALL ANGIOMATOUS MALFORMATIONS IN PRODUCTION OF INTRACEREBRAL HEMATOMAS. G. MARGOLIS, G. L. ODOM, B. WOODHALL, and B. M. BLOOR, J. Neurosurg. **8**:564, 1951.

The relation of large vascular anomalies to cerebral hemorrhage is familiar, but the role of small angiomatous formations in the production of intracranial hemorrhage is less well known. A survey of the problem of intracranial hemorrhage undertaken by the authors indicate (1) that a considerable proportion of hemorrhages are without demonstrable cause and (2) that small angiomatous malformations may play a more significant role than is usually recognized. Over a 20-year period, 14 hematomas of unknown cause and 9 cases of hemorrhage from angiomatous malformations were found, as compared with 29 hematomas resulting from berry aneurysms and 55 cases of hypertensive-arteriosclerotic apoplexy.

Six fatal hematomas related to vascular formations were studied at autopsy. The clinical and pathological features of these hemorrhages are described. Four were found to have been produced by rupture of small lesions. The minute size of one of these, the difficulty in demonstrating the second, and the deep-seated situation of the others point to their possible role in the production of so-called spontaneous intracranial hemorrhage. The incidental finding of two other cases of cerebrovascular lesions susceptible of being obliterated by related hemorrhage emphasizes this possibility.

ALPERS, Philadelphia.

Diseases of the Brain

FAMILIAL NATURE OF THE AMINO-ACIDURIA OF WILSON'S DISEASE. L. L. UZMAN and B. HOOD, Am. J. M. Sc. **392**:223, 1952.

Five asymptomatic members of a family of which four siblings died of Wilson's disease (hepatolenticular degeneration) were found to have persistent urinary excretion of amino acids even when on a protein-poor diet. There was also a considerable excretion of peptides of glutamic and aspartic acid. The suggestion is made that this familial metabolic disturbance of excretion of amino acids and peptides with dicarboxylic amino acids results in the cirrhosis of the liver seen in Wilson's disease.

BERLIN, New York.

ENCEPHALOPATHY OF HYPERINSULINISM. S. K. FINEBERG and A. ALTSCHUL, Ann. Int. Med. **36**:536, 1952.

Hyperinsulinism is here defined as the state produced by excessive amounts of insulin in the body, whether the insulin is exogenous or endogenous. Fineberg and Altschul state that hyperinsulinism is commonly seen as a result of the injection of overdoses of insulin, and rarely as a result of hypersecretion or disease of the pancreas.

The variability and multiplicity of symptoms seen in hyperinsulinism are well known. These characteristics of the condition appear to be related to the size of the initiating dose of insulin, the patient's inherent variability in response to insulin, the widespread areas of the brain which may be affected, and the particular phase eventually reached. All the symptoms appear to be encephalopathic in origin.

If the hypoglycemia is alleviated, the injury to the brain may prove of short duration and reversible; or, despite the attainment of hyperglycemia, it may be irreversible. In the latter instance, the permanent results of encephalopathy may be hemiparesis, ataxia, incontinence, aphasia, choreiform movements, Parkinsonism, epilepsy, mental deterioration, or idiocy.

The authors present four cases illustrative of the encephalopathy produced by severe hyperinsulinism. In the first, a change in personality resulted; in the second, mental deterioration, partial paralysis, and aphasia, and in the other two, death. In addition, a fifth case, in which encephalopathy appeared to be considerable but apparently complete recovery occurred, is described.

In general, the pathologic changes produced by excessive amounts of insulin consist of widespread decrease, alteration, and even complete destruction of neurones, especially of the cortex and basal ganglia; proliferation of the glial tissue, and petechial hemorrhages. These changes are not actually specific, but are sufficiently characteristic to be confirmatory when the history, clinical manifestations, and course have indicated hyperinsulinism.

The authors discuss the pathogenesis of hyperinsulinism in the light of the newer knowledge of carbohydrate metabolism and insulin physiology. They suggest the use of corticotropin and adrenocortical hormone if the encephalopathy does not respond immediately to glucose, and there appears to be danger of permanent cerebral damage.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

HEMANGIOMA OF THE SPINAL CANAL AND PREGNANCY. R. L. LAM, G. ROULHAC, and H. J. ERWIN, J. Neurosurg. **8**:668, 1951.

Vascular tumors of the spine and spinal cord are not uncommon, but they have rarely been noted as a complication related to pregnancy. A well-circumscribed extradural hemangioma of the upper dorsal segments is reported by Lam and his colleagues. The initial clinical manifestations appeared in the last trimester of the ninth pregnancy of a woman aged 36; there were subsequent remission symptoms and signs during the immediate postpartum period. Cessation of that improvement led to operation and complete removal of the tumor, with a remarkable recovery.

The authors discuss the exacerbations and remissions in symptoms in relation to mechanical obstruction to venous drainage as a result of the enlarged, pregnant uterus, and to possible estrogenic factors giving rise to increased vascularization.

ALPERS, Philadelphia.

A STUDY OF THE CAUSES OF FAILURE IN THE HERNIATED INTERVERTEBRAL DISC OPERATION. J. GREENWOOD JR., I. H. MCGUIRE, and F. KIMBELL, J. Neurosurg. **9**:15, 1952.

Of 632 cases in which Greenwood and his colleagues operated for herniated disk, reoperations have been done in 58. In nine additional cases the first surgical treatment was done elsewhere. These 67 cases of lumbar-disk herniation in which reoperation was performed are here reviewed from the standpoint of pathologic features and results.

From this study it becomes apparent that the operation for lumbar-disk herniation is not primarily one on the injured disk but one on the nerve root or roots involved. Reoperation is a worth-while procedure if proper notice is taken of this fact and will further reduce the number of failures.

The authors call particular attention to the value of making certain that the opening through which the nerve root must pass be at least 50% larger than the root itself, that there be no loose pieces of cartilage left behind, above, or below the interspace, attached to the nerve root or in the intervertebral foramen, and that no nuclear material be left in the intervertebral foramen. Bony prominences should be removed.

The results of nerve root section were fairly good. The success of fusion was unimpressive; fusion should be done, however, if no other direct result seems reasonable. The worst results were obtained in cases in which there was persistent or recurrent back pain without sciatic pain. Of the 67 cases, excellent or good results were obtained in 47; improvement resulted in 17, no improvement, in 3.

ALPERS, Philadelphia.

SECOND ATTACKS OF ACUTE ANTERIOR POLIOMYELITIS. A. T. COFFEE and W. D. PAUL, Neurology **1**:461, 1951.

Although admittedly rare, the occurrence of a second attack of paralytic poliomyelitis in the same person is unquestionable. The authors summarize 49 previously recorded cases of second attacks of acute anterior poliomyelitis and add 1 case of their own. In the case reported here two distinct attacks were separated by an interval of 24 years.

Coffee and Paul point out that the occurrence of additional symptoms, or the extension of previously existing motor impairment during the few months immediately succeeding an initial attack of acute anterior poliomyelitis, should be considered a recrudescence of existing infection. New symptoms occurring two or more years after the initial episode should be considered a reinfection.

Factors responsible for the occurrence of second attacks of poliomyelitis are as yet little understood. Possible explanations for the occurrence of several attacks of poliomyelitis are cited: 1. A second attack may be produced by a strain of virus antigenically unrelated to that which produced the initial infection. 2. Certain strains may fail to stimulate tissue or humoral antibody production. 3. Certain persons may be incapable of antibody production. 4. The body may lose its immunity in the course of time and therefore become susceptible to reinfection with a homologous strain. Any one or a combination of these factors may be operative in an individual case.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

INTRINSIC HEMANGIOMAS OF THE PERIPHERAL NERVES: A REPORT OF TWO CASES AND A REVIEW OF THE LITERATURE. E. J. LOSLI, A. M. A. Arch. Path. **53**:226 (March) 1952.

A number of cases have been reported in which hemangiomas involved peripheral nerves but were not primarily intrinsic. Since Sato reported his two cases of intrinsic hemangiomas of the peripheral nerves only three additional cases have been published which may be classified as authentic. Losli reports two cases of intrinsic hemangioma of the ulnar nerve, bringing the total number of cases recorded in the literature to seven.

An unusual lipide-containing lesion of the nerve is described. A plea is made that similar cases be reported and that the lesion be included in differential diagnoses and classifications of tumors of the peripheral nerves.

WINKELMAN, Philadelphia.

BELL'S PALSY. J. A. JAMES and W. RITCHIE RUSSELL, Lancet **2**:519 (Sept. 22) 1951.

James and Russell studied 58 cases of Bell's palsy. They suggest that this condition may develop as a result of compression of the nerve within the facial canal secondary to an inflammatory or vascular reaction in the neighborhood. With the pain, greater neck movements occur, which may increase the irritation of the stylomastoid blood vessels and further impair the blood supply. Thus, early administration of a vasodilator drug, or perhaps a sympathetic block and prevention of neck movements, is suggested as a possible therapeutic approach.

The clinical course follows one of two possibilities. In about 80% of cases, recovery begins within one to three weeks and is complete in four to six weeks. In 20% of cases the muscles remain completely paralyzed for two months or more, with degeneration of the facial nerve. The nerve is severely damaged, and recovery can take place only slowly by regeneration, generally at an interval of three to nine months from onset. Failure to recover at all is rare, but associated movements, which are an inevitable consequence of nerve regeneration, as well as some contractures, leave much to be desired so far as the cosmetic result is concerned.

MADOW, Philadelphia.

RETROBULBAR OPTIC NEURITIS DUE TO METHYL CHLORIDE. A. GARDE and R. ETIENNE, Rev. d'oto-neuro-ophtal. **23**:480, 1951.

A butcher aged 28 was examined for progressive diminution of visual acuity of two months' duration. In addition to diminution of visual acuity on both sides, defective color vision, as well as a central scotoma, was found bilaterally. The temporal half of both disks was pale. The patient smoked about a pack of cigarets and drank a quart of wine a day. Roentgenograms of the teeth revealed no foci of infection. Neurologic examination showed nothing significant. Roentgenograms of the skull and cervical portion of the spine showed nothing abnormal. The serologic reactions of the spinal fluid were negative. The patient had worked in a place where there was a defective frigidaire® for some time. Visual difficulties began soon after gas began to escape from this frigidaire® and became worse after the patient spent the whole afternoon in a room where the escape of gas was particularly marked. There was no improvement in spite of treatment with thiamine, strychnine, vasodilator placental extracts, cobra venom, and salicylates.

The authors have not been able to find a case of retrobulbar neuritis in the literature due to poisoning by methyl chloride. Methyl chloride is changed into methyl alcohol in the body. Methyl alcohol is known to affect the optic nerves.

N. SAVITSKY, New York.

Treatment, Neurosurgery

TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH PENICILLIN COMPARED WITH PENICILLIN PLUS AUREOMYCIN. M. H. LEPPER and H. F. DOWLING, A. M. A. Arch. Int. Med. **88**:489 (Oct.) 1951.

Of 43 patients with pneumococcic meningitis treated with massive parenteral doses of penicillin, 13 (30%) died. Of 14 similar patients treated with aureomycin in addition to the same dose of penicillin, 11 (79%) died. The last 14 of the 43 patients with pencillin therapy were treated alternately with the 14 patients given penicillin-aureomycin therapy. In this control group of 14 penicillin-treated patients there were 3 (21%) deaths.

There was no essential difference between the two groups with respect to age, number of organisms in the spinal fluid, mental status, portal of entry, pneumococcic complications, presence of other diseases, or day of disease on which therapy was started. The authors conclude that the poor results with the penicillin-aureomycin combination were not due to the chance inclusion of more severely ill patients in this group, nor did toxicity to aureomycin seem to account for the results. The evidence seems to favor the conclusion that penicillin and aureomycin are mutually antagonistic when employed together in the treatment of pneumococcic meningitis.

Consistently good results have been obtained in the treatment of pneumococcic meningitis with doses of 1,000,000 units of penicillin at two-hour intervals without use of the intrathecal route. Since good results have been obtained with aureomycin therapy alone in pneumococcic meningitis, further studies should be made on the efficacy of aureomycin, terramycin, and chloramphenicol, without adjuvant penicillin, in the treatment of this disease.

ALPERS, Philadelphia.

REACTIONS TO INTRATHECAL STREPTOMYCIN. R. J. MCKAY JR., J. A. V. DAVIES, W. BERENBERG, and H. M. LOWD JR., J. A. M. A. **147**:818 (Oct. 27) 1951.

There is still a popular concept, despite evidence to the contrary, that the intrathecal use of streptomycin in certain types of meningitis is both necessary and harmless. The authors report the occurrence of 14 serious reactions, with 3 probable and 2 possible fatalities, among 90 patients treated for meningitis. Repeated intrathecal injections of streptomycin were given to 65 patients with Hemophilus influenzae meningitis and to 25 patients with tuberculous meningitis.

The reactions consisted chiefly of shock-like states, with slow, irregular respirations, inability to handle adequately the secretions of the upper respiratory tract, convulsions, cerebellar signs, and sharp rises in body temperature, with peak severity usually appearing five to six hours after the intrathecal injection. The symptoms were not identical in each instance and

occasionally occurred immediately after withdrawal of the lumbar needle. There appeared to be some relation between the size of the intrathecal dose and the occurrence of reaction.

Mild reactions, consisting of pallor, irritability, loss of appetite, and stupor, occurred in a larger percentage of the cases. The nature of the signs and symptoms observed suggests that their etiology lies in a toxic action of streptomycin on medullary centers.

In the face of evidence that the intrathecal injection of streptomycin may cause serious toxic reactions, these workers believe there is a real contraindication to such treatment in any form of meningitis when equally good results can be obtained by some other mode of therapy.

ALPERS, Philadelphia.

PRESENT STATUS OF THERAPY IN MYASTHENIA GRAVIS. N. S. SCHLEZINGER, J. A. M. A. **148**:508, 1952.

Schlezinger reviews the current concepts regarding the pathogenesis of myasthenia gravis and reports on a survey of 65 patients treated during the past 10 years. He believes that combined neostigmine and ephedrine medication remains the treatment of choice for most patients with myasthenia gravis. Potassium and guanidine show a relatively slight beneficial effect in comparison with neostigmine, and undesirable side-effects limit their usefulness. Tetraethylpyrophosphate and octamethylpyrophosphoramide show a maximum therapeutic effect, approximating that of neostigmine but of longer duration. However, toxic reactions and difficulty in adjustment of optimum doses make their routine use impractical.

Two patients in this series had both myasthenia gravis and hyperthyroidism. In both these instances a complete remission of the myasthenia gravis developed coincident with the elimination of hyperthyroidism, by means of the use of methylthiouracil in one instance and of radioactive iodine in the other.

The author is of the opinion that the use of thymectomy should be resumed for patients with demonstrable thymoma and for a few selected patients whose myasthenia appears to be inadequately controlled with neostigmine and is not benefited by corticotropin therapy.

Four patients in this series and seven additional patients were treated with corticotropin. Corticotropin therapy results in relapse during the course of treatment, with noteworthy partial remission within 72 hours following termination of therapy. Subsequent relapse may occur, however, as it did in five of these patients, so that the ultimate therapeutic benefit is undetermined. The degree of improvement following repetition of corticotropin therapy in most instances did not equal the initial improvement. One patient, who had received a total of four courses of corticotropin therapy, died suddenly during an acute exacerbation of myasthenia gravis. It would appear advisable to refrain from the use of corticotropin in cases in which there is a tendency to repeated relapse after a relatively short interval of improvement.

ALPERS, Philadelphia.

INTRATHECAL TUBERCULIN IN TUBERCULOUS MENINGITIS. A. P. FLETCHER, Lancet **2**:290 (Aug. 18) 1951.

After the report of Smith and Vollum on the intrathecal use of tuberculin in treatment of tuberculous meningitis (these authors suggesting that part of the benefit of this agent might be the result of fibrinolytic action on the cerebrospinal exudate), Fletcher treated five patients with tuberculous meningitis who had responded poorly to conventional therapy with intrathecal injections of tuberculin. The results suggested that tuberculin treatment, instead of causing the lysis of exudate, may have contributed to its formation. In two cases fresh blocks developed during treatment; in a third a transient subtentorial block probably developed, and in two considerable progress of optic nerve atrophy occurred during treatment.

MADOW, Philadelphia.

News and Comment

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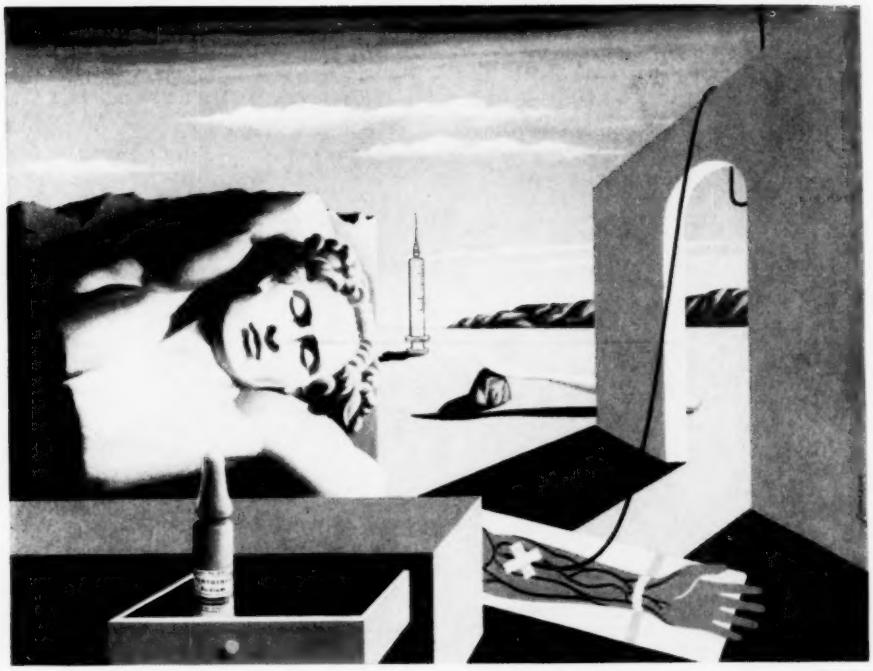
ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The annual meeting of the Association for Research in Nervous and Mental Disease will be held on Dec. 12 and 13, 1952, at the Hotel Roosevelt, New York. The subject of the meeting will be Metabolic and Toxic Diseases of the Nervous System.



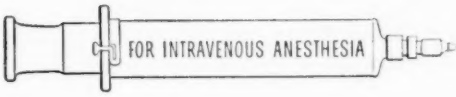
"Actually, it has not been so much a case of PENTOTHAL Sodium's supplanting other anesthetic agents and methods as it has been of complementing and supplementing them to the mutual advantage of one another."

Adams, R. Charles (1951), Intravenous Administration of Pentothal Sodium in Combination with Other Anesthetic Agents and Methods, J. Missouri Med. Assn., August.

IN minor and major surgery, for induction or induction and maintenance, *alone or in combination* with other anesthetics, PENTOTHAL Sodium continues to grow in popularity in operating rooms throughout the civilized world. Not without reason:

Eighteen years of experience, nearly 1900 published reports have shown that intravenous anesthesia with PENTOTHAL means a smooth, easy induction, generally without anxiety. And that deeper anesthesia may be had in a moment, as needed. Recovery is short, pleasant and usually without nausea. No bulky frightening equipment is needed. The fire and explosion hazard is eliminated. And, as it says above, this ultra-short-acting barbiturate complements and supplements other agents to "the mutual advantage of one another."

Abbott



PENTOTHAL® Sodium

(STERILE THIOPENTAL SODIUM, ABBOTT)